the
UNIVERSITY
of
TORONTO
MEDICAL
JOURNAL

NOV. 1965 VOL. XLIII NUMBER 1

PAEDIATRIC MALIGNANCIES

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the UNIVERSITY of TORONTO MEDICAL JOURNAL

Established December 1923
An Undergraduate Publication

Volume XLIII
Number 1
November 1965

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This Journal is published five times a year from November to March, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

SUBSCRIPTION RATES: $4.50 for one volume of five consecutive issues. Single copies, $1.00.

MANUSCRIPTS including references and footnotes should be typewritten double spaced on one side of the paper. Articles should not exceed 3,000 words. Canadian Press (American) spelling is to be used. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

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FINAL COPY DATE is the 15th two months prior to issue. Mailing date is the 15th of the month of issue.

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**CORRESPONDENCE should be addressed to: Room 109,
Medical Building,
University of Toronto,
Toronto 5, Canada.**

Authorized as second class mail by the Post Office Department, Ottawa, and for payment of postage in cash. Printers: Maple Leaf Press, Toronto, Ontario.

Editorials

This year's Medical Society decided that it would no longer be financially feasible to sponsor six issues of the University of Toronto Medical Journal. They decided that the April issue should be dropped. Therefore, we shall only be publishing five issues this year and we will incorporate the March and April editions into one issue.

Being editor of any publication is a very difficult job especially when it entails printing five issues comparable to last year's volume. At the national CAMSI conference held in Kingston during the Thanksgiving weekend, the University of Toronto Medical Journal was judged the best of all Canadian medical students' publications. This is a fine tribute to the work of the co-editors, Doctors Barry E. Koehler and Jerome S. Burke.

We have picked out six topics which we consider of interest and importance. This issue deals with the topic of Paediatric Malignancies. The writers have carefully studied and described various neoplastic diseases that afflict children. This topic was chosen because of the difficulty in finding a comprehensive, clear, and concise account in any standard text.

The associate editors have been excellent organizers and collectors of interesting articles. Their industriousness is reflected by their ability to obtain most of their writers and articles already. We must give special thanks to Emory Burkowitz for laying the ground work for the December issue.

We are introducing for the first time two comprehensive clinicopathological conferences. They will be appearing in the December and February issues. We are experimenting with this special feature and we hope that they will become a permanent feature in the journals of the future.

We cannot emphasize too strongly that the Medical Journal is published by the students for the students. The quality of the journal can therefore reflect only the interest and support of the undergraduates. It is our desire to maintain the Medical Journal's status as the best in Canada.

A.G.L.

Malignant new growths in children are the leading cause of death from disease in children from 2-14 years of age and because of this have in the last 10 years assumed a role of increasing importance among doctors caring for children. About 1/3 of these children suffer from leukemia and for these only temporary control can be obtained, but the other 2/3 of patients suffering from solid tumours are now offered a greater chance of living a normal life span. This greater opportunity has come about through the better use of surgery and radiation and the introduction of chemotherapeutic agents. A major portion of this improvement has been the result of earlier recognition of the disease on the part of the physician and the abandonment of a position of hopelessness and "laissez faire". In the past unfortunately this latter was the attitude of many doctors when faced with a child who was suffering from cancer.

The physician is obliged now not only to be aware of the problem, but must know how it best can be handled to give the greatest chance for life with a minimum of handicaps for the patient in the future. When the child has an incurable form of disease, the problem can be even more difficult. The family must receive the support essential for them to face the burden. This support should be provided by the physician in whom they trust, and this can be provided best by the physician whose knowledge is widest and whose understanding is greatest.

Dr. J. M. Darte

Acute Leukemia

K. W. Johnston 6T6

Leukemia is a disorder characterized by (1) generalized uncontrolled proliferation of white blood cells and their precursors in blood forming organs, (2) invasion of organs in which the cells are not normally found, and (3) a clinical course which (at the present time) progresses to death.[6 7 26] Inherent in this definition are distinctions from the lymphomata which are localized proliferations of white blood cells and from leukocytic reactions which are controlled white cell proliferations. On the basis of this definition, it is apparent that the word leukemia ("white blood") is a misnomer since the blood need not be "white" (the WBC count may be normal or decreased) and the "blood" is not involved primarily but rather leukemia is a disease of the blood forming tissue.[7]

CLASSIFICATION

Three parameters are used simultaneously to classify a case of leukemia.[7]

(1) Degree of Differentiation and Clinical Course

—acute: rapid proliferation of undifferentiated ("blast") cells usually associated with a short clinical course (days, weeks, or months)

—chronic: slow proliferation of predominently differentiated cells with a longer clinical course (months or years)

(2) Lineage[6 7]

—lymphatic and stem cell: according to some authors in children acute stem cell leukemia and acute lymphatic leukemia are synonymous terms.

—granulocytic (myeloid)

—monocytic - Schilling type (reticulum cell origin)
- Naegeli type (myeloblast origin)

—plasmocytic

(3) WBC Count

—leukemic: leukocyte count elevated

—subleukemic: normal or low leukocyte count but primitive WBC seen in blood; 55% of children present with WBC count less than 20,000.[3 5]

—aleukemic: normal or low WBC count and no abnormal primitive cells seen in the peripheral blood.

—preleukemic leukemia: occurs primarily in older people and may be diagnosed only in retrospect. In this entity after months or years of anemia, neutropenia, or thrombocytopenia with no apparent bone marrow abnormality, leukemia develops.[1 6]

INCIDENCE

In children, leukemia is the commonest malignant disease, representing about one third of cases[34] (in adult 4.6%[30]) and is the commonest fatal disease in the age group 4 - 14 years.[15] 96% are acute (adult 60%[7 27]). The cell type is lymphatic (synonymous with stem cell) in about 95% of cases. The peak age incidence for acute lymphocytic leukemia is 3 - 4 years (66% of cases occur under 5 years) and for acute myelogenous leukemia, under 1 year and over 12 years.[10] The sex ratio is 3 males : 2 females.

PATHOGENESIS

Athough several factors are known to cause leukemia in animals, at present, the cause of leukemia in man remains speculative. The following etiological factors have been implicated:

(1) *Viral infection.* To date, 14 viruses have been described which cause murine leukemia.[3] Virus particles have been demonstrated in the plasma of leukemic animals and similar but as yet unclassified virus-like particles have been found in the plasma of patients with acute leukemia.[15] It is possible that the virus particles seen in man do not cause leukemia but infect and proliferate in a leukemic host because his resistance is low.[15] In animals, leukemia is easily transferred with cell free extracts but in man transfusions of even large amounts of leukemic blood do not transmit the disease.[31]

(2) *Ionizing radiation* will cause leukemia in animals and in man may be contributory in some cases. There is a higher incidence of leukemia among radiologists (8-9x), Japanese atomic bomb victims (10-50x), polycythemic patients treated with P^{32}, and in patients who received radiotherapy for ankylosing spondylitis or thymic enlargement.[23] The type of leukemia which develops following radiation is myelogenous and appears after a latent period of 2 - 15 years.[15]

(3) *Genetic.* In mice, certain strains have a high incidence of spontaneously developing leukemia, and in man the occasional case has been sited to illustrate the possible significance of heredity. In chronic myelogenous leukemia the Philadelphia chromosome (deletion of part 21 or 22) is the same chromosome affected in mongolism (extra 21 or 22), and the incidence of chronic myelogenous leukemia is higher in Mongols.[15]

(4) Numerous other possibilities have been suggested: e.g., the existence of some unidentified substance which would result in a maturation arrest similar to that seen in pernicious anemia, the presence of a chemical capable of inducing leukemia (eg. benzene[23]), a failure in the normal process of removing WBCs.

Whatever the cause, immature leukocytes become autogenous, incapable of maturing, and no longer responsive to normal leukocytic control mechanisms. These changes may occur at the level of DNA or at the cytoplasmic level.[7]

The disease begins in hematopoietic tissue (bone marrow or reticuloendothelial tissue) as a diffuse hyperplasia without evidence of abnormal cells.[8] As the disease progresses, foci of leukemic cells appear in the bone marrow, and with further proliferation the foci enlarge, become confluent and replace the normal marrow producing evidence of marrow failure (anemia, thrombocytopenia, and functional leukopenia) and bone damage. From bone marrow the cells infiltrate throughout the body. In individual organs leukemic infiltrates often first appear as perivascular aggregates from which the parenchyma is invaded.[31] Cells infiltrating the liver in acute leukemia may be localized to the portal areas as in chronic lymphatic leukemia or spread to become diffuse resembling the picture of chronic myelogenous leukemia.[7] In the spleen the pulp is involved and the lymphatic elements obliterated. Lymph nodes enlarge as the architecture is destroyed by infiltration or localized proliferation in the lymphatic types of leukemia. Central nervous system leukemia has many forms—infiltration of nervous tissue, intracranial hemorrhage, meningeal plaques, infiltration, and obstruction of Virchow-Robin spaces.[7 33 36] Retinal changes include white nodules surrounded by hemorrhages, engorged retinal veins, and perivascular sheathing.[25] In the oral cavity, petechiae are frequently evident, leukemic infiltration results in gingival hypertrophy (especially in the monocytic type) and the gums often bleed, become infected and ulcerate.[12 31]

The lungs are rarely affected but may show peribronchial infiltrations. Renal infiltrates are usually diffuse.[35] The skin shows evidence of marrow failure (anemia, petechiae or ecchymoses) and is occasionally involved directly with macular or papular infiltrates (leukemia cutis).[31] Bony trabeculae become more slender and the periosteum thickens as new bone is laid down in response to irritation from leukocytic infiltration. Chloromas, green masses of tumour cells usually associated with acute granulocytic leukemia, are found most often in relation to the bones of the face and skull.[7]

SYMPTOMS

There are no specific symptoms of acute leukemia. The common types all have similar clinical pictures. In a child, acute leukemia usually presents abruptly[7 21 37] with constitutional symptoms of fever, lassitude, or weakness and any of the following pictures:

1. Presentation as Marrow Failure. (Symptoms resulting from the anemia, functional leukopenia, or thrombocytopenia of bone marrow failure are the most common and are evident to some degree in most cases). Thrombocytopenia and subsequent hemorrhage account for the presenting symptoms in 55% of children[18] (26% of adults[20]). Purpura is the most common manifestation but other epithelial membranes may be affected producing (in order of frequency) epistaxis, bleeding gums, hemoptysis, melena, menorrhagia, retinal hemorrhage, conjunctival hemorrhage, hematemesis, or hematuria.[22] "Functional agranulocytosis"[6] produces an infection with fever (continuous or intermitten) which is slow to respond to treatment in 75 - 100% of cases.[7 23] Fever, as in the lymphomata may also be the result of the basic disease process. Anemia causes lassitude, energy loss and if more severe, shortness of breath.

2. Rheumatic Presentation. In children there is little yellow marrow, and consequently the marrow cavity is replaced rapidly, and direct bony infiltration occurs early. As a result bone pains and tenderness are a common presenting symptom. The pains may be steady or intermittent and may be referred to the joints. These symptoms, together with joint swelling from synovial infiltration may clinically be indistinguishable from acute rheumatic fever or Still's disease.

3. Glandular Presentation. Lymph node enlargement is usually minimal, mimicking infectious mononucleosis or one of the lymphomata.

4. CNS Presentation. This presentation is not common; however, since currently used chemotherapeutic agents fail to penetrate the blood brain barrier leukemic infiltration of the CNS occurs at some time in the disease in 20 - 50% of patients.[33 36 41] Headache, vomiting, convulsions, etc., may simulate brain tumour or meningitis.

5. Dental Presentation. A dentist may be consulted initially because of bleeding gums, gingival hypertrophy or ulceration.

6. Abdominal Presentation. Abdominal pain may simulate any of the causes of "the acute abdomen". Abdominal pain is frequently present but may not in itself be the presenting symptom.

7. Other possible presentations are virtually limitless because of the diffuse nature of the disease.

SIGNS

The findings on examination of children with acute leukemia are highly variable, and in some cases there may be no signs demonstable. In general, however, the child appears ill with evidence of hemorrhage, pallor, continuous or intermittent fever, with or without obvious infection. Conjuctival or vitreous hemorrhages, papilledema, venous dilation, or retinal hemorrhages with characteristic pale centres may be seen in the eyes. The gingiva are often hypertrophic, bleeding or ulcerated. The spleen is palpable in 70% of cases[21] and the liver is usually enlarged. There is slight lymphadeno-

pathy in 75% of children.[24] CNS signs when present are very variable and may include signs of meningeal irritation, focal damage to nervous tissue, or increased intracranial pressure. Bones may be tender, and joints may be swollen. Ecchymoses, petechiae or purplish macular or papular infiltrations (leukemia cutis) occur in the skin.

LABORATORY INVESTIGATION

Hematological investigation is necessary in every case to establish the diagnosis.

Peripheral Blood. Anemia is usually present. The red cell morphology is that of a normochromic normocytic anemia with slight anisocytosis, slight to moderate reticulocytoses, and a variable number of nucleated red cells. Platelets are usually decreased. The leukocyte count is usually subleukemic or leukemic and only rarely aleukemic. Blast cells are typically present in great numbers and a neutropenia is present. When the lineage cannot be readily distinguished the following may be of help: (1) Auer bodies, azurophilic rods in the cytoplasm of blast cells (probably representing coagulated granules)[30], are present in 50% of cases of acute myelogenous leukemia but not in the lymphoblastic type. (2) The peroxidase reaction is positive in some cases of acute myelogenous leukemia if the cells have differentiated to the promyelocyte stage. (3) The type must often be implied from other primitive cells present in the blood film. The erythrocyte sedimentation rate is usually greatly increased.

Bone Marrow is usually hypercellular and replaced with blast cells, but up to 20% are in the aplastic state. 5 - 10% blasts may occur in a leukemoid reaction. Red blood cell precursors and megakaryocytes are reduced.

Blood Chemistry. Renal and liver function tests may be abnormal. Calcium and alkaline phosphase may be elevated in the presence of bony involvement.

Cerebrospinal Fluid in cases of CNS leukemia exhibits a pleocytosis, elevated protein, decreased glucose and leukemic cells.

Radiographs may demonstrate mediastinal modes, pleural effusions, or bone lesions.[21]

DIFFERENTIAL DIAGNOSIS[7 28]

Leukemia can simulate an endless number of other diseases but the following hematological disorders present perhaps the greatest problem in differential diagnosis. (1) *Infectious mononucleosis* is an infectious disease characterized clinically by the acute or gradual onset of fever, symptoms of an upper respiratory infection, cervical lymphadenopathy (or elsewhere), splenomegaly, or pneumonitis, pericarditis, hepatitis, aseptic meningitis, encephalitis or a macular-papular skin rash. In contrast to leukemia, infectious mononucleosis is characterized by a normal hemoglobin, normal platlet count, slightly elevated leukocyte count (2-4X), absolute lymphocytosis with each cell being morphologically different from the next, normal bone marrow and an increased Paul Bunnell reaction. (2) *Leukemoid reaction* refers to the presence of immature leukocytes in the blood or a decreased, increased or normal WBC count.[4] It most commonly occurs in pertussis, typhoid fever, infectious lymphocytosis, other acute infections, and bone marrow involvement with secondary cancer. Usually it can be distinguished from leukemia which has 60 - 70% blasts, anemia, thrombocytopenia and an abnormal bone marrow, but in some cases the eventual clinical course is the only distinguishing factor. (3) *Idiopathic thyombocytopenic purpura* presents with megakaryocytes which are normal or increased in number although morphologically abnormal, and other marrow elements are normal. (4) *Henoch-Schönlein purpura* shows no hematological manifestations. (5) *Aplastic anemia* may be difficult to distinguish from acute leukemia since both may have a hypocellular marrow; however, the diagnosis of leukemia can usually be made on the basis of splenomegaly, lymphadenopathy, marrow examination along with the presence of anemia, thrombocytopenia and leukopenia.

COURSE OF DISEASE AND PROGNOSIS

Without treatment acute leukemia in children is progressive with death usually resulting from hemorrhage or infection.[11] The median survival is 2.7 months with variations from days to 16 months.[38] Spontaneous remissions occur temporarily in 10% of untreated patients most commonly after adrenal stress (febrile illness, hemorrhage, etc.) and have a mean duration of 6 weeks (same length as steroid induced remissions).[35 38]

Current treatment induces remissions in 80 - 90% of children and prolongs survival significantly. With remissions, symptoms and signs disappear, and blood and bone marrow become normal, or almost so. The disease recurs in weeks or months, and subsequent remissions become harder to induce and less complete. 50% of patients survive 10 - 14 months and 10% 21 - 28 months.[42] In 1964, 56 children with 5 year survivals were collected from the literature.[17]

MANAGEMENT

The therapy of a child with acute leukemia involves (1) management of the parents, (2) supportive treatment, (3) chemotherapy and (4) radiotherapy.

1. Management of the Parents[13 40]

The parents must know the diagnosis and although the mention of the word "leukemia" on the first visit may seem unnecessarily harsh, they should be told initially that their child is suffering from leukemia, a serious disease of the blood, bone marrow, and other organs for which there is no known cure. They should be re-assured that it is not contagious and that they are in no way responsible, and should be cautioned

TABLE 1 — MECHANISM OF ACTION AND POINT IN CELL CYCLE

Drug Name	Mechanism of Action	Point in Cell Cycle
Prednisone	Unknown (destroys lymphocytes?)	?
Vincristine	During mitosis binds spindles preventing separation during metaphase.	M
Methotrexate	Folic acid antagonist. Binds to the enzyme folic acid reductase with much greater affinity than does folic acid; hence folic acid is not converted to folinic acid which is required in the synthesis of purines and pyrimidines for DNA manufacture.	S
6-MP	Incorporated into DNA and RNA in place of the normal purine base.	S (when into DNA); all phases (when into RNA)
Cyclophosphamide	Nitrogen mustard derative. Neoplastic cells supposedly contain higher concentrations of the enzyme phosphamidase which will split cyclophosphamide releasing pure nitrogen mustard which produces cross linkages between DNA chains preventing normal division.	M?

about disclosing it to too many "friends" for fear that the child will be informed accidently. Most important, the parents should understand that with current drug treatment the child's disease will, in all probability, remit for a variable period of time, and he will appear perfectly normal and should be so treated.

2. Supportive Treatment[16]

Supportive therapy involves the control of hemorrhage, infection and renal failure.

Hemorrhage is corrected with platelet rich plasma (plasma from fresh centrifuged whole blood), a platelet concentrate or fresh whole blood if there is an associated anemia.

The presence of infection is often difficult to diagnose since fever is also a manifestation of the leukemic process and since the usual signs of inflammation may be absent because of steroid suppression and bone marrow depression. Freireich recommends antibiotic therapy only after the sudden onset of fever. Leukocyte transfusions from patients with chronic myelogenous leukemia are still experimental.

Renal tubular obstruction resulting from hyperuricemia may cause renal failure. It may be prevented by ensuring a high urine output and alkalinizing the urine. Should renal failure occur mannitol may reverse it; otherwise, dialysis is necessary.

CHEMOTHERAPY

The currently available chemotherapeutic agents are capable of prolonging life and producing a complete remission in a large percentage of patients — that is, abolishing all clinical symptoms and signs, rendering the peripheral blood and bone marrow normal. In general, children less than 2 years and adults over 30 years of age respond poorly.[19] Acute lymphatic types of leukemia show good responses, whereas acute myelogenous and acute monocytic are more resistant.[19 28]

The Antileukemic drugs useful in the treatment of acute leukemia are (1) prednisone, (2) vincristine (3) amethopterin (Methotrexate), (4) 6-mercaptopurine (6-MP), and (5) cyclophosphamide (Procytox).

These agents Act at different stages of the cell cycle and the leukemic cells are killed because they are more rapidly proliferating. It will be recalled that the cell cycle consists of the following stages: M phase (mitosis) lasting 20 - 30 minutes; G1 phase (first rest stage) lasting a variable length of time; S phase (DNA synthesis) lasting 6 - 8 hours; and G2 phase (second rest phase) lasting 4 hours. The mechanism of action of each drug in relation to this cell cycle is summarized in Table 1.

The Current Treatment of acute leukemia in children is founded on the information in Table II. Prednisone or vincristine induces remissions rapidly (1 month) in a high percentage of cases (50 - 60%) but induces the remission for a relatively short period of time (2 months). In contrast Methotrexate, or 6-MP or cyclophosphamide induce remissions more slowly (1 - 2 months), in fewer patients (20 - 35%) but maintain remissions longer (5 - 6 months).

On the basis of this information, it is evident that to induce a remission prednisone or vincristine or both are the most useful. With the combination of prednisone and vincristine remissions are obtained in 70 - 80% of cases.[10-14]

TABLE II[10-14 37]

Drug Name	Start Remission	Remission Complete	Median Duration Remission	% Complete Remissions	% Complete & Partial Remissions
Prednisone	1 D	3 W	2 M	57%	80%
Vincristine	1 D	4 W	1.5 - 2 M	50%	55 - 85%
Methotrexate	3-21 D	4 W	6 M	22%	45%
6-MP	14-35 D	8 W	6 M	35%	54%
Cyclophosphamide	1 D	8 W	5 M	20%	10 - 25%

For MAINTENANCE THERAPY the following possibilities are open: no further treatment until relapse; continuing prednisone or vincristine; or more often using Methotrexate or 6-MP or Procytox. When the disease RELAPSES the drug on which the patient relapses is discarded and prednisone or vincristine or both are used to induce a remission again and then maintenance is attempted with one of the remaining drugs.

In an attempt to entirely abolish the leukemic cell compartment, combined drug therapy has been advocated.[17] Complete remissions can be induced in 88% of patients with the combination of vincristine, amethopterin (Methotrexate), 6-MP, and prednisone—the so-called VAMP routine. The toxicities of the drugs are additive and during this treatment the patient must be kept in a "sterile island" to minimize the risk of infection.

The treatment of CNS leukemia is worthy of separate mention because of the morbidity and mortality it causes, frequently while the disease is in remission. The preferred therapy at present is intrathecal Methotrexate or if this fails, radiation.

The SIDE EFFECTS of chemotherapy in general are related to the systems with the most rapid cell proliferation: (1) bone marrow — thrombocytopenia with bleeding, neutropenia with possible infection, and anemia only after very long usage; (2) gastro-intestinal tract — nausea and vomiting, diarrhea, and mouth ulcers; (3) skin and appendages — alopecia; (4) other — neuritis with vincristine, all the dangers of steroids, and hematuria and dysuria with Procytox.

4. RADIOTHERAPY

Radiotherapy may offer palliation in some of the following situations: skin infiltrations, central nervous system complications (after intrathecal Methotrexate has been tried), bone pain if adequate trial of chemotherapy fails, or mediastinal masses.[9]

Whole body radiation alone (200 - 300r) or with bone marrow transplantation when supralethal doses are given (800 - 1000r) has been tried on an experimental basis but remissions have rarely been greater than 3 - 4 months.[9] Because of the relatively poor results and because experimental work suggests that leukemic cells are quite resistant to radiation[7 37] thus making it impossible to sterlize the patient with clinically practical doses of radiation, it is felt that whole body radiation with bone marrow transplantation has no place in the current treatment of leukemia.[7 9]

SUMMARY

Acute leukemia is the commonest malignant disease of childhood. It is usually the leukemic or subleukemic acute stem cell (lymphatic) type. Etiology and pathogenesis are considered. The disease presents clinically with evidence of bone marrow failure (anemia, hemorrhage, or fever), rheumatic complaints, nodal involvement, CNS symptoms, dental complaints, or with abdominal pain. On examination the patient is typically anemic, febrile and has hemorrhagic manifestations, hypertrophic, bleeding and ulcerated gums, lymphadenopathy, splenomegaly, hepatomegaly, and occasionally signs of CNS, bone, or skin involvement. The peripheral blood film and bone marrow examination confirm the diagnosis and distinguish leukemia from infectious mononucleosis, leukemoid reactions, aplastic anemia, idiopathic thrombocytopenic purpura, Henoch-Schölein purpura, and the numberous other diseases that must be considered in the differential diagnosis. Supportive treatment, chemotherapy and radiotherapy are discussed. Without treatment the median survival is in children 2.7 months but with currently available methods 50% survive 1 year and 10% 2 years. During a remission the child is usually perfectly normal but inevitably the disease remits and at present is progressively fatal.

ACKNOWLEDGEMENT

The author wishes to thank Dr. M. Souley and Dr. J. M. Darte for their assistance in the preparation of this paper.

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Abstract

The Surgical Management of Transposition of the Great Vessels

W. T. Mustard, M.D., J. D. Keith, M.D., G. A. Trusler, M.D., R. Fowler, M.D. and L. Kidd, M.D.: The J. of Thor. and Card. Surg., Vol. 48, No. 6, December 1964, pp. 953 - 958.

Without treatment, an infant born with transposition of the great vessels rarely survives his first year. This article outlines a two stage surgical method of total correction of this condition. The first stage is the early creation of an atrial septal defect as suggested by Hanlon and Blalock in 1948. The second stage, carried out during the second or third year of life, is to place a baffle made of endogenous pericardium so that pulmonary venous return is directed into the right ventricle and blood returning from the systemic circulation into the left. Placement of the baffle allows for growth and ensures relatively normal hemodynamics. The article, with illustrations, describes the technic for positioning the baffle to achieve these ends.

Infants with transposition of the great vessels are considered in three categories.

(1) Those with a patent foramen ovale and patent ductus arteriosus.

(2) Those with an atrial septal defect and a patent ductus.

(3) Those with foramen ovale, patent ductus and ventricular septal defect.

Treatment for group (1) is the creation of an atrial septal defect and then at two years, when the heart is large enough, the insertion of a baffle. Treatment for group (2) is the insertion of a baffle at about two years. These children will usually survive this period without developing irreversible pulmonary vascular changes. However, patients in group (3) are prone to cardiac failure in the first year or the related development of irreversible pulmonary vascular damage.

In the experience of the authors, of seven children suitable for stage two correction, (those without irreversible pulmonary vascular changes), six appear normal and well five to seventeen months following surgery.

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Central Nervous System Tumours In Children

C. C. Wells 6T6

Prior to the development of modern neurology and neuropathology, the clinical differentiation between the various intracranial lesions was very difficult. Anti-syphilitic treatment was available and a trial of this was often employed for suspected intracranial lesions in the hope that it might provide a cure.[2]

Subsequently it became possible to localize the lesions to major areas of the brain. The development of ventriculography by Dandy and the newer diagnostic methods including arteriography and radioisotopic scanning make it possible today to localize tumours fairly accurately and sometimes give some idea of their pathology.

The types of intracranial lesions have also changed. Whereas today the gliomas make up the majority, Starr[12] in 1890 estimated the tuberculomas accounted for approximately 50% of the total and Critchley[3] in 1925 reported that these were still the commonest and that the gliomas followed in second place. Today tuberculomas are rare in most parts of the western world.[8]

GENERAL CONSIDERATIONS

Incidence

Intracranial tumours represent about 20% of pediatric malignancies.[5] In the United States in 1961, the mortality for children aged 1 - 14 years due to malignant neoplasms was 8.1 per 100,000.[13] This indicates the relative importance of intracranial tumours.

In 1927 Cushing found that brain tumours in children were about one sixth as common as in adults; however, Ford feels that with newer methods of diagnosis the incidence of these tumours in children is higher and in fact almost as high as in adults.[6]

The peak incidence of childhood tumours appears to be toward the end of the first decade. The numbers then drop to a minimum at about 16 years of age.[2] This is probably due to the large number of medulloblastomas seen in early childhood followed by a decreasing incidence of childhood tumours prior to the onset of the more usual adult types.

There is little significant difference between the two sexes with the exception that medulloblastomas and possibly the pinealomas occur more often in males.[4]

Site

Prior to the turn of the century it was known that the majority of intracranial tumours were located infratentorially in children whereas the opposite was true in adults. Most authors report that approximately 65 - 70% occur beneath the tentorium.[1 2 4 8] There is a tendency for the tumours to be located along the midline.

Tumour Types

The vast majority of the primary intracranial tumours are gliomas. In most series they account for approximately 80% of the total.[1 2 4 8]

Dargeon[4] compiling the results of a number of authors reports the following incidence among 1102 cases:

astrocytomas — 34%
medulloblastomas — 26%
ependymomas — 13%
mixed gliomas — 5%
craniopharyngiomas — 7%

The remainder were glioblastomas multiformes, choroid plexus papillomas, hamartomas, haemangiomas, teratomas and dermoids, gliomas of the optic chiasma as well as other ever rarer types such as fibrosarcomas, pinealomas and cerebral neuroblastomas.

As is seen in other forms of neoplastic disease, there is a considerable difference between the types of intracranial tumours found in children and in adults. In adults, gliomas account for only about 45% of the total, and the midline cerebellar gliomas, which are so common in children, are rarely seen. Also the more common types of adult tumours such as meningiomas, acoustic neuromas and pituitary adenomas are hardly ever found in children.[8] Another important difference between children and adults is that secondary brain tumours are rare. Occasionally one finds secondaries from Wilms' tumour, neuroblastoma, Ewing's sarcoma and leukaemia.[4]

Common Signs and Symptoms

1) *Due to Local Involvement*

Convulsions and motor and sensory changes of which the first indication may be given by disturbances of gait or weakness of a limb are seen as in adults. Midline and lateral cerebellar lesions may result respectively in truncal ataxia and ipsilateral limb signs. Specific cranial nerve signs especially strabismus and other eye signs such as a decrease in visual fields or acuity are also seen. Children may also present with growth re-

tardation and other manifestations of hormonal imbalance such as precocious puberty or genital hypoplasia.

2) *Due to Increased Intracranial Pressure*

These signs and symptoms may be seen with any tumour which expands rapidly or blocks the cerebrospinal fluid circulation. They are particularly common in the posterior fossa tumours.

(a) Vomiting is a very common sign, occurring espepecially in the early morning and not accompanied by nausea.

(b) Headache may occur again especially in the early morning and usually wears off as the day progresses. This is often described as being frontal in location and may occur with any tumour but is especially characteristic of lesions in the cerebral hemispheres.[4]

(c) Papilloedema is especially common and is seen even in cases where the cranial sutures have not yet fused.[8]

(d) Rapidly enlarging head relative to the rest of the body, Macewen's "cracked pot" sound, bulging fontanelle, and venous dilation may be seen.

(e) Changes in disposition may be the only early signs and of course are hard to interpret. The child may insidiously become more irritable, drowsy, lethargic and start to do poorly at schoolwork. These signs are especially important in the cerebral hemisphere tumours.

Diagnostic Test

The diagnostic tests used are similar to those employed for adults. However, as the history obtained from children may be quite inadequate, relatively more importance must be placed on the tests.

1. Plain X-Rays of the skull are of great importance. Calcification, asymmetry, and bone erosion are localizing signs, and separation of the cranial sutures, erosion of the posterior clinoid processes, and prominent emmissary veins indicate increased intra-cranial pressure.

2. Pneumoencephalography is helpful especially to outline the cisterns if a tumour is suspected in the region of the optic chiasma. Extreme caution must be taken if increased intracranial pressure is present.

3. Ventriculography is useful especially in tumours of the cerebral hemispheres and also for doubtful cases of posterior fossa tumours. The extent of a craniopharyngioma may also be outlined. At this time the cerebrospinal fluid can be examined for protein content and cytology.

4. Electroencaphalography is now used mainly to differentiate idiopathic epilepsy from other causes where children have had focal seizures.

5. Angiography is helpful especially for tumours of the cerebral hemispheres as in adults. In older children the percutaneous injection technique is used while in smaller children it may be necessary to expose the artery directly.[8]

6. Radioisotopic scanning is now used extensively in adults. The accuracy of localization of posterior fossa tumours is lower than that of tumours of the cerebral hemispheres. This fact and the unknown long term effects of the radiation have contributed to delay the acceptance of this form of investigation routinely in young children.

TREATMENT

Surgery

The treatment of choice of most intracranial tumours is complete surgical excision and where this is not possible, as much of the tumour as can be removed safely should be removed. Dargeon[4] feels that all suspected primary tumours except possibly pinealomas, brainstem and pontine tumours require operation and exploration. Although a more malignant variety of tumour may be suspected a biopsy should be obtained to avoid the tragedy of overlooking a more benign curable tumour. Pressure relieving shunt procedures may be employed where resection of a tumour blocking the cerebrospinal fluid circulation is impossible.

Radiation

The main use of radiation is as a sequel to surgery where excision has been incomplete. It is particularly useful in treating the very radiosensitive medulloblastomas where recurrence is the usual rule. In many instances where radiation fails to kill completely the remaining neoplastic cells it may nevertheless offer good palliation.

Chemotherapy

Oral antimetobolites have not been shown to help; however, intrathecal amethopterin may be of some help in medulloblastoma,[4] and local arterial perfusion is being tried for some tumours.

PROGNOSIS

The prognosis varies greatly depending on the type of tumour, its location, its extent, and its adherance to vital surrounding structures.

Benign, surgically accessible tumours including many dermoids, teratomas and cerebellar astrocytomas can often be totally excised and thus cured completely. Even when cerebellar astrocytomas were only partially removed, Gol and McKissock[7] report a 5 year survival of 9 out of 16 cases.

With most of the other tumours the prognosis is on the whole poor. Glioblastoma multiforme is hopeless

but fortunately rare. Medulloblastomas usually recur throughout the cerebrospinal axis but Darte[5] feels more complete cures are possible with irradiation. Tumours of the brain stem carry a very poor prognosis since they cannot be removed without damage to vital centres.

SPECIFIC TUMOURS

The specific tumours will be considered under the following headings:

1. Posterior cranial fossa tumours
   (a) Cerebellar astrocytoma.
   (b) Medulloblastoma.
   (c) Ependymoma.
   (d) Gliomas of the brain stem.
2. Gliomas of the cerebral hemispheres.
3. Craniopharyngiomas.
4. Intracranial dermoids and teratomas.
5. Others.
6. Intraspinal tumours.

1. *POSTERIOR CRANIAL FOSSA TUMOURS*

(a) *Cerebellar Astrocytoma*

Incidence

One series of 185 posterior fossa tumours in children under 12 years showed 30% to be cerebellar astrocytomas.[8] They are the second most common posterior fossa tumour and their incidence reaches a peak between 5 and 8 years. In another series of 98 cases of this tumour, 73% were found in children 15 years and under.[7] Males and females were affected equally.

Signs and Symptoms

These are relatively benign tumours and signs and symptoms tend to develop slowly and may continue over two years although great variation is possible.[1] They are typical of the posterior fossa group and may present with vomiting and headache especially in the morning, made worse by stooping and straining. Disturbances of gait and nystagmus are often the first cerebellar signs.[7] Papilloedema is an almost constant sign.[7 8] An enlarging head and Macewen's sign are also common. Cerebellar fits (attacks of unconsciousness associated with increased intracranial pressure and opisthotonus) occur in approximately 11%.[7] On the whole symptoms appear earlier in those in whom the tumour lies in the midline.

X-Rays often show separation of the cranial sutures but calcification is rare.[8]

Pathogenesis

These slow growing tumours have a tendency to lie in the midline but may extend into the cerebellar hemispheres. Approximately one third are midline, one third occupy the vermis and one hemisphere, and the remaining third are lateral.[7]

They have a great tendency to form cysts with often only a small nodule of tumour on one wall. Gol and McKissock found that 85% of their series were cystic and contained 4-100 ml. of fluid.[7]

The solid type tend to extend both downwards into the spinal canal as well as upwards into the cerebellar nuclei, peduncles, and along the aqueduct of Sylvius and even into the third ventricle. It is this type especially which may adhere to adjacent structures and thus darken the prognosis.

The microscopic picture is that of a diffuse arrangement of uniform astrocytes in a loose stroma with little evidence of vasculature.[8]

Treatment

This is almost entirely surgical. Well differentiated astrocytes are not affected by irradiation; however, even with incomplete surgical excisions, a long symptom free interval is usually obtained because of their slow growth.[8] Complete radical removal may be achieved in about 65% of cases.[7]

In some of the less well differentiated non-cystic types where extension into the brain stem has precluded total excision, post operative irradiation may be of some benefit.[5]

Prognosis

These are the most favourable of all the gliomas since there is the possibiliy of complete excision combined with their slow growth. The mortality is highest in the midline tumours where a higher proportion are the solid type and are more likely to be adherent.[7]

(b) *Medulloblastoma*

Incidence

These are the second most common intracranial tumours in children. They tend to occur relatively early in life, with a peak incidence reported at 3 years. In one series of 68 cases, 41 were male and 27 were female.[8]

Signs and Symptoms

These are generally typical of the posterior fossa tumours; however, a slightly greater number of cases show normal eye grounds and skull X-Rays compared with the cerebellar astrocytomas. Truncal ataxia may result from their common midline cerebellar location. The onset of signs and symptoms is however much faster since these are among the most rapidly growing posterior fossa tumours. The average duration of symptoms is 4-6 weeks.[8] This is also due partly to the location of the tumours, often on the anterior medullary velum, since blockage of the aqueduct or the fourth

ventricle may occur while the tumour is still quite small giving early signs of increased intracranial pressure.

Pathology

These tumours are almost always located in the midline but may extend into the cerebellar hemispheres. They commonly grow into and fill the fourth ventricle and may even appear out of the foramina of Luschka and Magendie.

There is no line of cleavage between tumour and surrounding tissue; however, they are relatively soft and a large portion can usually be sucked out at operation. They are relatively vascular tumours and occasionally are cystic.

Microscopically they are very cellular with no regular pattern and little stroma.[8] The origin of these tumours is not known definitely but may be from the cells of the external granular layer of the cerebellar folia.[11] Medulloblastomas have the ability to seed themselves throughout the whole cerebrospinal axis and separate tumour nodules may be found throughout the meninges.[8]

Treatment

Complete surgical excision is usually impossible; however, immediate symptomatic relief from increased intracranial pressure is best accomplished by surgical correction of the cerebrospinal fluid circulation. If this cannot be visualized or corrected, a bypass shunt should be employed to relieve the pressure.

As much tumour as can be removed safely should be excised. Primary irradiation is not justified since a biopsy is necessary to confirm the diagnosis. Primary irradiation without some surgical decompression may even result in some temporary expansion of the tumour with further damage to surrounding structures. Also children with papilloedema may lose their vision very rapidly and if this occured during a trial period of radiotherapy it would be a tragedy.[8]

Post-operative irradiation should be administered to the whole central nervous system with the hope of obtaining a cure or at least delaying the return of symptoms. This may be accomplished by using a lead shield with a suitable cut-out to expose the brain and spinal cord.[5]

Prognosis

In the past most writers have considered the prognosis of medulloblastoma to be hopeless; however, Darte feels that this attitude should be changed and that some cures are now possible with modern radiotherapy.[5]

(c) *Ependymoma*

Incidence

Ependymomas are the third commonest tumours after medulloblastomas and astrocytomas in the posterior fossa.[8]

Signs and Symptoms

Signs and symptoms are relatively slow to develop in this group since these tumours are slow growing and are not highly invasive. They may produce all the typical signs and symptoms of posterior fossa tumours. Ependymomas also have a tendency to extend down the spinal canal and cause local pressure which may result in neck stiffness or an abnormal position of the head or pain radiating down the neck and shoulders especially on movement of the head.[2]

Pathology

Their origin from the ependymal cells means that they may be attached closely to the floor of the fourth ventricle, and often this is in the region of the calamus scriptorius. They are generally firmer and less vascular than the medulloblastomas, and cyst formation is rare. Occasionally calcium is laid down and may show up on X-Ray.[8]

Microscopically many polygonal cells surround the blood vessels leaving a clear band which represents the cell processes extending to the vessel wall. Stroma is usually abundant.

Treatment

In those with close attachment to the floor of the fourth ventricle, complete surgical removal is impossible without damaging some cranial nerve nuclei, restiform bodies, or nuclei of the dorsal columns.[1] However, their avascularity lends the rest of the tumour to piecemeal removal so that the obstruction to the cerebrospinal fluid can be removed.[8]

The well differentiated ependymomas respond poorly to irradiation. The less well differentiated ones are more radiosensitive and have a tendency to seed themselves along the cerebrospinal axis similarly to the medulloblastomas and therefore irradiation therapy similar to that employed in medulloblastomas may be considered.[5]

(d) *Gliomas of the Brainstem*

Incidence

In Ingraham and Matson's series of 313 intracranial tumours, 10% were diagnosed as brainstem gliomas. There is a peak incidence at 5-6 years and males and females are affected approximately equally.[8]

Signs and Symptoms

These tumours differ from the other posterior fossa tumours in that there is usually no blockage to the cerebrospinal fluid circulation and therefore no increased intracranial pressure. As a result the tumour may grow

unnoticed for longer periods of time.[1] The duration of the history averages 1-5 months.[8]

An almost diagnostic syndrome of space occupying lesions in the brainstem is that of multiple bilateral cranial nerve abnormalities together with pyramidal signs and truncal ataxia in the absence of increased intracranial pressure. The cranial nerves most often affected are 5 to 9 and sometimes 12.[8] Plain X-Rays show almost nothing. Ventriculography may show a slight dilation of the lateral ventricles, and the aqueduct and floor of the fourth ventricle displaced upwards and backwards.

(a) Tumours in the region of the midbrain may produce signs of involvement of the corpora quadrigemina such as loss of associated upward eye movement, loss of pupillary light reflex and nystagmus. There may be severe and unexplained drowsiness or cerebellar signs. If the red nucleus is affected, a course tremor in the opposite arm may appear.

(b) Tumours of the pons may cause conjugate deviation of the head and eyes. Involvement of the pontocerebellar fibres may give unsteadiness of gait and station. Limb spasticity, urinary retention, or incontinence are common. Sensory symptoms are generally late to appear.

(c) Tumours of the medulla are rare, but extension into this region may be seen with tumours originating in the pons. Vomiting, vertigo, and respiratory disturbances occur early as well as cardiac arrhythmias and swallowing difficulties. Other signs are voice changes due to soft palate weakness, and limb spasticity from pyramidal involvement.[6]

Pathology

The type of tumour generally found is a slow growing astrocytoma, a spongioblastoma, and rarely a glioblastoma multiforme.[6]

Treatment

The location of these tumours adjacent to vital structures makes their removal impossible and exploration dangerous. Even biopsy may be contraindicated due to the hazard.[4] These tumours are not curable by irradiation; however, this form of treatment may help to suppress symptoms and make the child temporarily more comfortable.

Prognosis

The prognosis is hopeless with average survivals of less than one year in spite of any treatment.[8]

2. *GLIOMAS OF THE CEREBRAL HEMISPHERES*

Incidence

This group accounts for 10-14% of all the intracranial tumours in children.[1,8] They may occur throughout all the childhood years with perhaps a slight peak at two years of age.[8] Males are affected more than females.

Signs and Symptoms

These tumours, like the posterior fossa group, may cause increased intracranial pressure and the earliest signs may result from this. Headache is especially common.

Focal signs are more important in these gliomas although these may be difficult to evaluate in children since many cortical areas may not have become fully developed. Such signs as hemianopia, cortical anaesthesia, aphasia, and apraxia etc. may be readily apparent in older children but are harder to assess in younger ones. Thus one may have to depend more on such motor signs as hemiplegia, focal weaknesses, or focal convulsions.[6]

Also important but hard to interpret at the time is the change in the child's disposition which may accompany the tumour. Listlessness, indifference to friends, and lack of normal enthusiasm are examples of this.[8]

The paucity of definite physical signs means that diagnosis is often delayed and may not be made until the tumour is quite large.

Electroencephalography is helpful where convulsions have occured without any localizing signs. X-Rays commonly show suture separation and sometimes localized erosion of one frontal or parietal bone or sphenoid wing. Ventriculography by air injected through the separated coronal suture, is quite reliable.[8]

Pathology

Astrocytomas are the most common type of glioma found in the cerebral hemispheres and account for 40%. These are mainly solid types and are usually fairly well demarcated from the surrounding tissue.

Ependymomas account for about 25% and have a greater tendency to cyst formation. Due to their origin from ependymal cells, they tend ultimately to encroach on the ventricular lumen although extension may occur anywhere in the hemisphere. Occasionally calcification is seen on X-Ray.

Glioblastoma multforme makes up only about 15% of these gliomas in children compared to a higher incidence in adults. These are among the most malignant and rapidly growing tumours of the central nervous system. They are not encapsulated, are usually deep seated, and infiltrate extensively.[8] They may even extend from one hemisphere to the other by way of the corpus callosum.[6] Microscopically they show great variation in cell size and multinucleated cells and mitoses are seen. Areas of haemorrhage, degeneration, necrosis, and calcification are common.[8]

Other types encountered are medulloblastomas, mixed gliomas, oligodendrogliomas, microgliomas and astroblastomas.

Treatment

Radical surgical excision is the preferred treatment. Tumours not completely removed, especially glioblastoma multiforme, may be temporarily slowed down by post-operative irradiation.[5]

3. *CRANIOPHARYNGIOMA*

Incidence

This tumour accounts for only 5-13% of all intracranial tumours.[1] It may manifest itself at any age although the majority have their onset before the age of 20 years.[2]

Signs and Symptoms

The location of these tumours results in signs and symptoms of increased intracranial pressure, visual disturbances due to optic chiasmal involvement, and manifestations of pituitary and hypothalamic dysfunction. Signs of increased intracranial pressure are more common in younger children and endocrine disorders are more common in older children and adults.[1] Pituitary involvement mainly results in growth disturbances, i.e. normally proportioned "pituitary dwarfs". Extreme cases occasionally show the picture of Simmond's cachexia.[8] Involvement of the posterior hypothalamus may be indicated by drowsiness or subnormal temperatures whereas anterior hypothalamic involvement may result in polyuria and polydipsia.

Skull X-Rays are almost always abnormal. Approximately 60-70% show flecks of calcium representing the solid part of the tumour. The sella itself may be distorted. Ventriculography is helpful for determining the extent of the tumour; often air may be injected directly into the cyst. The absence of pituitary adenomas in childhood further simplifies the diagnosis.[2]

Pathogensis

Craniopharyngiomas develop from squamous epithelial cell rests in the stalk attaching the posterior pituitary to the hypothalamus.[4] Almost all are cystic, either uni- or multi-loculated.

Treatment

Complete surgical removal may be possible initially but excision of recurrent tumour is rarely possible due to adherence of the cyst capsule to adjacent structures such as the pituitary gland, circle of Willis, or optic chiasma. The cyst should be aspirated and as much of the suprasellar portion removed as possible surgically. Repeated aspirations may be necessary if symptoms return. Postoperative irradiation probably does not stop tumour growth but may slow down the rate of fluid reaccumulation.

Prognosis

This is worse in the younger ages due to a higher incidence of third ventricular involvement. Complete cures are now often possible.

4. *INTRACRANIAL DERMOIDS, EPIDERMOIDS AND TERATOMAS*

This is a small group totalling about 5% of the intracranial tumours. The dermoids and teratomas tend to lie in the midline while the epidermoids more commonly lie laterally.

(a) *Dermoids and Epidermoids*

These may originate from epithelial cells misplaced during the separation of the neuroectoderm from the epithelial ectoderm and therefore the defect may extend from the skin into the brain or even into the central canal.

Signs and Symptoms

A mid-line tumour may be suspected if a skin dimple, tuft of hairs or dermal sinus is found. Cysts near the skin surface may be palpated, and if infection has occured, signs or inflammation may be present. When these cysts are located in the occipital region they may mimic the symptoms of cerebellar or fourth ventricle tumours, or hydrocephalus due to other causes. The connection between skin and nervous tissue implies a skull defect which may or may not be large enough to be demonstrated by X-Rays.

Pathology

The dermoids are usually cystic containing fluid with cellular debris, sebaceous material, and sometimes hairs. The cysts have a stratified squamous epithelial cell lining surrounded by a fibrous capsule.

Treatment

Complete surgical removal of cyst, sinus tract, and skin dimple if present may lead to a complete cure. If the capsule is adherent to adjacent tissue, a subtotal removal may be all that is possible.[9]

(b) *Teratomas*

These strange tumours are the result of misplaced proliferation of totipotential cells.[1] They may represent part of a second individual.[6]

Signs and symptoms are very varied as these tumours may occur widely spread throughout the brain.

Pathologically they are slow growing tridermal tumours. Malignant change is not common but fear of this justifies their early removal.

The treatment is complete surgical removal where possible. Close proximity to the third ventricle may render this difficult.[1]

5. *OTHER INTRACRANIAL TUMOURS*

(a) *Choroid Plexus Papillomas and Papillary Adenocarcinomas*

These uncommon tumours occur mainly in childhood. They arise from either the glomus of the choroid plexus in the lateral ventricle or less commonly from the choroid plexus in other locations.

These do not usually invade nervous tissue and therefore localizing signs are usually absent. Signs and symptoms are mainly those due to increased intracranial pressure, since their location commonly results in obstruction of the cerebrospinal fluid circulation which is produced in excess quantities.

Ventriculography is most helpful in outlining these tumours. The treatment is complete surgical removal where possible. This may be particularly hazardous with tumours in the fourth ventricle, especially since they may extend out of the lateral recess. Post-operative irradiation is employed in malignant cases.

(b) *Gliomas of the Optic Pathway*

Gliomas in this location are seen mainly in childhood and early adolescence. These gliomas are mainly mature, benign, slow growing types such as the astrocytomas which are common in the brain.

Those located intraorbitally usually present with visual disturbances accompanied by unilateral proptosis. Intracranial lesions more commonly produce visual loss and signs of increased intracranial pressure. One third of the cases show stigmata of generalized neurofibromatosis.

The preferred treatment usually consists of transfrontal craniotomy and orbital unroofing and excision of the tumour. Where removal is incomplete, post-operative irradiation should follow.[1]

(c) *Tumours of the Meninges*

The meningioma, so common in adults, is rare in children. Occasionally sarcomas of the leptomeninges and fibrosarcomas of the dura are encountered, usually showing signs of increased intracranial pressure or convulsions. The prognosis is usually hopeless.

6. *INTRASPINAL TUMOURS*

Incidence

Intraspinal tumours occur only about one fifth as often as intracranial tumours in children. Most cases are seen in children over nine years of age.[4]

Signs and Symptoms

The commonest symptoms are weakness of a limb and backache. These may cause a noticeable reluctance to bear weight or a gait disturbance. Root pain following dermatomes is rare since tumours of the nerve roots and their meninges are seldom found in children compared with their higher incidence in adults. Sphincter incontence may result from a tumour but may be difficult to differentiate from normal during the training years. Skin dimpling may indicate an underlying dermoid cyst.[10] These are more common in younger children.

Lumbar puncture is important since total cerebrospinal fluid protein is almost always raised. Plain X-Rays may show up spinal abnormalities which may accompany the congenital dermoids and teratomas. Myelography is very helpful to demonstrate the level of the lesion as in adults.

Pathology

Three broad groups of tumours are seen in children.

(a) The congenital types such as the dermoid cysts and teratomas. Microscopically they resemble the corresponding intracranial types.

(b) The intramedullary gliomas which roughly parallel those in the brain. Astrocytomas are most common, followed by ependymomas. These are more frequent in boys.[10]

(c) The third group is made up of the extradural extensions of paraspinal tumours. These may include neuroblastomas, reticulum cell sarcomas, lymphosarcomas, and others. They may grow into the spinal canal through the intervertebral foramen and cause cord compression.

Treatment

Complete surgical excision where possible is the ideal treatment. Laminectomy in the growing child carries more risk of deformity than in adults and therefore braces or plaster casts may be required for long periods post-operatively.[8]

Radiation therapy has relatively little place except to delay recurrence of cord compression following incomplete removal of the more malignant tumours.[1]

RETINOBLASTOMA

Retinoblastomas are congenital malignant tumours arising from the nuclear layers of the retina. They develop from multiple foci, often in both eyes, and are the commonest and most malignant neuroectodermal tumours of the retina. The average age of appearance is thirteen months, the sexes are affected equally, and bilateral involvement is seen in one third to one half of the cases.[18] It is transmitted by a single rare autosomal gene of high but incomplete penetrance. Forty to fifty per cent of survivors' children will be affected.[14] Falls and Neel estimate a spontaneous mutation rate of one in 20,288 births.[15]

These tumours resemble medulloblastomas and peripheral neuroblastomas in malignancy and cellular characteristics. Two types occur: a) the commoner tumour composed of undifferentiated retinoblasts which may form pseudorosettes, and b) the rare type composed of spongioblasts which may form true rosettes.

Local extension may be into the vitreous, the endophytum type of tumour, or subretinally, the exophytum type. Tumour cells may scatter throughout the eye and implant and grow wherever nutrition is adequate. The surface of the vascular choroid is particularly favourable in this respect. There is a tendency to invade the optic nerve but extension beyond a few millimetres is rare. Metastases may appear in the skull, bones, lymph nodes, viscera, and spinal cord.

Spontaneous regression has been recorded and may be the result of the tumour outgrowing its blood supply.[18]

Signs and Symptoms

Frequent presenting features are leukocoria, esotropia, or a family history of the disease. The eye is usually normal in size but the creamy pink coloured lesions may be seen through the pupil. Diagnosis may be difficult in the hidden exophytum type.

Calcium is an important diagnostic feature and roentgenograms, particularly special oblique bone-free views, indicate the diagnosis. Cytological study of the subretinal fluid or the aqueous may help in making the diagnosis.[18]

Treatment

a) Unilateral tumours are often far advanced and the preferred treatment is enucleation with the removal of as long a stump of the optic nerve as possible.[16]

b) Bilateral tumours are usually handled by removing surgically the worst eye and treating the remaining eye if it is felt that vision can be saved.[18] Treatment by a combination of radiation and chemotherapy is felt to be more effective than radiation alone.[17] Appropriate treatment consists of betatron therapy preceded and followed by triethylene melamine (TEM), 0.08 mg/Kg. In severe cases the TEM. is given intraarterially, in others it is given intramuscularly.[16]

Light coagulation is usually reserved for cases that fail to respond to radiation and TEM.[18]

c) Residual tumour left after enucleation is probably treated best by radiation and intraarterial TEM.

d) Recurrent tumour is treated by exenteration of the orbit, followed by radiation and intraarterial TEM.[18]

Prognosis

This to a considerable extent depends on the extent of the lesion at the time of diagnosis. With radiation and TEM. therapy 90% of the most favourable group of cases are cured and even 20% cures are obtained in the very unfavourable group with extensive ocular involvement.[16]

ACKNOWLEDGEMENT

The author is indebted to Dr. H. Hoffman and Dr. J. C. McCulloch for their helpful suggestions and assistance.

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"On experimental studies, through the manoeuver of placing a small window in the skull of the animal, I was able to observe, with direct vision, the effect of increasing the pressure within the skull. I found that if at any time intracranial pressure exceeded the arterial pressure, circulation failed and the animal died."

Thus wrote a young surgeon named Cushing who later, almost single-handedly, brought the field of neurosurgery into the limelight.

Harvey Cushing was born in Cleveland, Ohio on April 8, 1869. In high school his best grades were in mathematics. He attended Yale College but one cannot contend that this made a serious student of him. His friends recall that he was more interested in baseball, the gym and girls. Financial problems loomed large throughout his college career as his father could not afford to be lavish with the tenth child of the family. In addition to being active in sports, he loved to visit the circus and see the "freaks" at the side shows . . . and it was Cushing who later first proved how giants and dwarfs came to be.

In September, 1891 the young man entered the Harvard Medical School. He tackled his work with a great vigour. An example of his keeness to learn is contained in a letter which he wrote to his father.

"I have settled my fate as far as the Christmas holidays are concerned. I will not be home as I have accepted an opportunity to work in the Out-Patient Department of the General Hospital."

During his career as a medical student, Cushing often served as an anaesthetist for various surgeons. One of the first patients he anaesthetized died before a large class of students . . . a circumstance which had profound effect on the sensitive young man and caused him to devise, with Amory Codman, improvements which are still in use in operating theatres today. There was, at that time, no convenient device for estimating blood pressure, so that when Cushing, several years later, saw a pneumatic device in Italy he brought it back to the States. Thereafter his "ether charts", as the anaesthetic records of Codman and Cushing had come to be called, included a continuous blood pressure record in addition to pulse and respiration.

Following graduation, Cushing was assigned to a convalescent home in Waverly. Contact with the mental and neurological cases there did much to crystallize his interest in Neurology. In the autumn of 1896, the young man moved to Baltimore to take up duties as W. S. Halstead's Assistant Resident in Surgery at John Hopkins Hospital. Cushing's early training under Halstead had profound influence on the development of his career as a surgeon. In later years he stated that the greatest lesson he had learned from Halstead was never to do anything to a patient without understanding why.

At John Hopkins, Cushing was responsible for introducing X-rays for clinical work. On November 6, 1896 a woman entered the Emergency Department, having been shot in the neck by her bartender husband. The bullet had entered the cervical region and was lodged somewhere in the neck. Cushing took X-rays with a primitive machine and then wrote his first paper on this case.

Shortly after this, Harvey Cushing began to become widely known to the general public as a brain surgeon. Prior to this many general surgeons had made casual attempts to operate on the brain but persistent failure had discouraged them. In England, Victor Horsley alone had persevered despite disheartening losses. Though he had started some fifteen years before, his surgical technique did not reach anything approaching the careful ritual of the Cushing school.

In 1900, an important neurological case came under Cushing's care in the person of the great astro-physicist, Simon Newcomb. The problem was meralgia paraesthetica. The brilliant neurosurgeon's description of the operative procedure read this way.

"His operation went well enough and there was no difficulty in finding the nerve, though the old gentleman was quite abdominous. He insisted on propping himself up on his elbows every now and then to see what we were doing, but unfortunately his centre of gravity intervened. Despite this disappointment however, he was much elated and kept up a running conversation throughout the procedure."

From 1908 to 1912 one finds Harvey Cushing at the peak of his activity. His attention during this period was focused on the normal functions and clinical disorders of the pituitary gland, and on the surgical treatment of tumors. During this period Cushing had operated three times upon an unusual patient . . . a girl who presented herself complaining of headaches and failure of vision. He noticed incidentally, that the patient was fat, and that, although fourteen years of age, she had failed to mature sexually. He decompressed the brain on both sides, and although headache was gone, vision still deteriorated. Thinking that she might be suffering from a tumor in the back of the head, he made a cerebellar exposure at a third operation and the patient died. At the autopsy he was chagrined, and profoundly interested to discover the presence of a large pituitary cyst.

He made a detailed description of the condition which bears his name today . . . Cushing's Syndrome.

Following a period of service overseas during which he made great technical contributions to wartime surgery, Cushing went back to neuro-surgery at home and to writing a biography of Sir William Osler whom he had so much admired.

By 1931, Cushing had removed his 2000th verified brain tumor and soon after, retired from the operating theatre. He returned to Yale, his old school, as professor of Neurology for the period from 1933 to 1937. On October 3, 1939, after attempting to shift a heavy folder, a severe attack of substernal pain occurred. He was taken to hospital and placed in an oxygen tent to which he strenuously objected because he could not see out.

And there, shortly after, Harvey Cushing, scientist, surgeon and pathfinder, died, leaving his shining example for others to follow.

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Wilms Tumour

J. J. E. Turley 6T6

Wilms tumour is a congenital tumour arising from the kidney and found in infancy and childhood. It has been called embryoma, myosarcoma, adenomyosarcoma, nephroblastoma, Birch-Hirschfield tumour and a host of other names, but perhaps the best is embryonal mixed tumour of the kidney. It should not be confused with the hypernephroma or Grawitz tumour which is most common in later life and almost unknown in childhood.

Wilms tumour was first recognized in 1828 by Gardner. In 1894 Birch-Hirschfield described and emphasized the multiple types of tissue, and in 1899 Wilms wrote the classical description of the tumour.

INCIDENCE

Wilms tumour and neuroblastoma together make up 20% of childhood malignancies. Wilms is second only to leukemia in the malignancies found in children less than 5 years of age. Although the tumour is congenital, it is rarely detected at birth. Two-thirds present before 3.5 years of age, and they are seldom seen beyond the first decade of life, although a few cases have been reported in late adult life. Males and females are equally affected. An unusually high incidence of congenital abnormalities in children with Wilms tumour has been reported particularly aniridia and anomalies of the genitourinary tract.

ORIGIN

It is now believed that the tumour arises from the primitive mesenchyme in which the definitive kidney develops—the metanephrogenic blastema. The tumours differ in the degree of differentiation and in the number of tissues represented, and therefore they must originate at different developmental stages in the embryo. A tumour arising when the nephrotome is predominant will contain recognizable renal structures, whereas a tumour that develops earlier when the cells have a greater potential for differentiation will elaborate multiple tissues.

PATHOLOGY

The tumour usually arises in the substance of the kidney and is at first enclosed in the renal capsule and separated from kidney tissue by a fibrous investment. Very rarely, it occurs as a separate encapsulated retroperitoneal mass. There are a great variety of sizes, the largest reported recently being 22 pounds. Grossly, it a rounded or nodular solid mass. The cut section is grey white and soft with vascular, medullary, gelatinous, edematous and cystic areas separated by bands of fibrosis. It is often necrotic and hemorrhagic in parts. The mass grows rapidly and distorts and may invade the renal pelvis. Microscopically, there may be undifferentiated and embryonic cells, abortive renal tubules and glomeruli, fibroblastic tissue, or aberrant mesoblastic elements such as muscle, cartilage, or bone. It is a vascular tumour with many thin walled capillaries. The mass contains only elements derived from mesenchyme and is not a teratoma.

The tumour spreads by the blood stream and lymphatics, and lung and liver are by far the most common sites of metastases. Skeletal metastases do occur but are relative rare compared to the neuroblastoma. The cells not infrequently invade the vein massively and grow into the inferior vena cava. By direct extension, the mass may destroy the walls of blood vessels and the ureter, but direct extension through the capsule of the kidney into surrounding structures occurs relatively late. Up to 10% of reported cases have bilateral renal tumours either discovered simultaneously or becoming apparent within a few months. It is not known whether bilateral masses represent two primary tumours or metastatic spread. In a recent consideration, Jagasia concludes that bilateral Wilms tumours rarely represent metastases.

CLINICAL PRESENTATION

By far the most common mode of presentation is an asymptomatic mass found in the abdomen of an infant accidentally by the parents or on routine medical examination. The mass may attain recognizable proportions very suddenly or increase in size rapidly because of hemorrhage into the mass. Careful questioning will sometimes disclose that the child has been pale or irritable for some months, but this is exceptional. Pain is a relatively rare symptom and usually takes the form of some vague poorly localized discomfort. More severe pain may occur if blood clots pass through the ureter, or the mass increases rapidly in size and exerts pressure on the renal capsule. Urinary symptoms are also rare. Hematuria is a late finding in 10 - 25% of cases (75 - 85% of adult tumours produce hematuria) and is generally felt to indicate a poor prognosis. Some authorities feel that hematuria results from hemorrhage into the parenchyma of the congested kidney, but others believe that it indicates invasion of the renal vein or the kidney pelvis by tumour. Fever spiking to 101 - 104°F is quite common and occasionally is the presenting complaint. It persist while there is active tumour present and increases as a terminal complication. Other symptoms usually occuring with advanced disease are anorexia, vomiting, constipation, weight loss, restlessness, irritability, and pallor. Cough and pleural pain produced by lung metastases may present.

Usually the only physical finding is a smooth spherical or oblong well-defined mass arising in the loin and only occasionally crossing the midline of the abdomen. It is often fixed and does not move in relation to the posterior abdominal structures with palpation or respiration. Hypertension and anemia are usually found only in advanced disease.

The most important aid in diagnosis is the intravenous pyelogram. A plain film of the abdomen almost always shows an opaque mass with enlargement of the kidney shadow and displacement of the intestines to the middle or opposite side of the abdomen. Calcification is common the neuroblastoma and appears as a fine stippling throughout the mass. Calcification is only seen occasionally in Wilms tumour and takes the form of dense homogenous streaks and concentric rings in the periphery of the tumour. The IVP may show impairment of ipsilateral renal function; but some evidence of dye excretion is almost always seen on the involved side so that a change in shape and displacement of the renal pelvis can be demonstrated. A lateral film may help to differentiate an extrinsic mass displacing the kidney from an nitrarenal tumour. It is also important to determine the function of the contralateral kidney by pyelography before treatment is undertaken. A chest film should be done because of the relatively high frequency of pulmonary metastases already present when the tumour is first found. Biopsy probaby should not be attempted prior to nephrectomy as it ruptures the capsule and promotes peritoneal seeding. It should be reserved for those rare cases in which the diagnosis is doubtful and surgery is contraindicated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes:

1. Masses of Renal Origin: these are spherical flank masses that increases the size of the renal silhouette, distort the renal pelvis and are usually not calcified; for example,

a. Hydronephrosis is very common. It usually is the result of congenital obstruction at the ureteropelvic junction or ureterovesical valve. It may present at an asymptomatic mass, but it is usually accompanied by pain, fever and pyuria. IVP or retrograde pyelogram is almost always diagnostic.

b. Renal cyst or polycystic kidney may trans-illuminate and has a characteristic appearance on x-ray.

c. Other kidney tumours—renal cell carcinoma, lymphoma, hemangioma—are very rare.

2. Nonrenal Masses: they tend to be nodular and fixed and extend beyond the midline. The renal silhouette may be displaced but it is normal in size and shape unless invaded. The ureter may be displaced, but the renal collecting system is not distorted. Calcification is common.

a. Neuroblastoma is another common abdominal tumour of infancy and childhood. The infant presents with an abdominal mass which is firm, round, pebbly surfaced and poorly defined. Skeletal metastases are common; lung metastases are rare.

b. Retroperitoneal teratoma is a solid or partially cystic mass that may arise anywhere along the posterior abdominal wall.

c. liver neoplasms
splenomegaly
gynecological lesions-ovarian tumours
lymphomas
appendiceal abscess
mesenteric cyst

The most common lesions in the differential diagnosis are splenomegaly, neuroblastoma, and hydronephrosis.

TREATMENT

There are three means of treating Wilms tumour—surgery, radiation and chemotherapy, and each has been used alone and in combination with the others. There is still some controversy about the optimum method of treatment largely because most series of reported cases are quite small.

SURGERY

It is generally agreed that surgical intervention is necessary whenever possible and that any delay may favour dissemination of neoplastic cells by unskilled handling of the child, too frequent palpation, accidental abdominal trauma, spontaneous rupture of the capsule of the tumour or spontaneous embolization of the tumour cells to distant sites. The principles of management, therefore, are act quickly, do minimal studies—blood counts, IVP, chest x-ray-palpate as little as possible. The tumour should probably be removed as an emergency procedure within 24 hours of hospital admission. An abdominal transperitoneal incision is made an the renal vessels are identified, tied, and divided; the kidney, the tumour and usually the adrenal gland are removed en bloc with the surrounding fat and fascia. In contrast to neuroblastoma where abdominal spillage is not to grave, the prognosis of Wilms tumour decreases considerably if the abdominal cavity is contaminated with tumour at the time of operation. It is usually not possible to do a block dissection of the regional nodes in continuity; they are usually simply biopsied, but if resection of the tumour is not too traumatic and the patient is in good condition, dissection of the nodes may follow removal of the primary neoplasm. The possibility of involvement of both kidneys should be kept in mind at operation in order to detect a small contralateral lesion while it may be extirpated without sacrificing too much normal kidney. (Jagasia[11] in his 1964

review of bilateral Wilms tumours suggests further that an IVP be done routinely at 6 and 12 months to detect a tumour in the other kidney early.)

RADIATION

The radiosensitivity of this tumour is well established. Radiation alone, however, is not advisable because there is not histological verification of the malignancy of the mass and results are poor. It should be reserved for patients who refuse surgery or in whom surgery in contraindicated.

Radiation is therefore given in combination with surgery since the cure rate is better than with nephrectomy only but there is some disagreement about the timing of radiation in relation to the operative attack. Klapproth[13] in an analysis of 1351 cases treated in different centres between 1940 and 1958 found little difference in the prognosis whether radiation was preoperative, postoperative or both pre and post operative, but in most series the best cure rate is obtained with nephrectomy followed by radiation. Preoperative radiation has the following advantages: 1. it shrinks large tumours, and 2. death of tumour cells prevents spread at the time of operation. Disadvantages are: 1. operative delay, 2. the mass may increase in size during the period of radiation, 3. the tumour may metastasize in the weeks during which radiation is being given, 4. the possibility of accurate diagnosis is decreased, and 5. a child may occasionally be heavily irradiated for a benign lesion. Preoperative radiation enjoyed some popularity when the operative techniques were inadequate and the renal vein was not tied early in the operation, but it is now reserved for huge fixed tumours in most buy by no means all centres (cf. Vaeth[25]). Postoperative irradiation is done routinely in most centres. While awaiting period of 3 to 10 days is advised by some radiotherapists to allow normal healing of the operative wound, others advise beginning therapy as soon as the incision is closed with the patient still anaesthetized. Late postradiation problems that occur occasionally are nephritis, retardation of bone growth, impairment of hemopoiesis, dysfunction of ovaries and irradiation pneumonitis. These can largely be avoided by proper planning of fields for therapy with shielding of ovaries, opposite kidney and lungs and symmetrical radiation of the spine to avoid growth deformities.

Radiation is also beneficial in the treatment of abdominal recurrences and distant metastases. Pulmonary metastases respond rapidly and completely to radiation in low dosage—in fact up to 14% 5 year survival is reported—and the dose can be repeated when the lesions recur, but the effect is less with each exposure. Some authorities therefore advise that lung lesions should be radiated only when they give symptoms and not on first appearance. Abdominal recurrences and contralateral renal masses also respond well to radiation.

CHEMOTHERAPY

A large number of chemotherapeutic agents have been used in the treatment of both the primary tumour and distant metastases. Nitrogen mustard, folic acid antagonists, ACTH, cortisone, and sex hormones have all proven ineffective. The most useful drug currently available is an antibiotic, Actinomycin D. Actinomycin interferes with the synthesis of pantothenate in lactobacillus organisms; in man it may interfere with the synthesis and/or biological activity of coenzyme A or inhibit the formation of RNA. When actinomycin is given in conjunction with irradiation, an increased skin effect as compared with the effect of radiation alone is observed, and previously irradiated sites are reactivated if the interval between treatment and subsequent doses of the drug is not too long. It is therefore believed that the effect of irradiation is enhanced or potentiated by Actinomycin D. In metastatic Wilms tumours, about 1/3 of patients seem to experience a striking response, but remission is short in most cases. Because the true efficacy of the drug is still unknown, many modes of administration are being used at present. In some centres 75 micrograms/kgm is being given routinely in 5 divided doses, one on the day of operation and one on each of 4 succeeding days; in others it is used 2-4 hours prior to radiation every other day for the duration of radiation treatment; in others, it is used exclusively for the treatment of distant metastases or cases in which operative removal is known to be incomplete. Toxicity occurs in nearly all patients in the form of ulceration of the tongue and buccal mucosa, nausea, vomiting, anorexia, abdominal pain, diarrhea, alopecia, vesiculation and exfoliation of radiated skin, leukopenia and thrombocytopenia and possibly late genetic effects. Bone marrow depression may necessitate reduction in the total dose of radiation given, and this is the chief argument against the routine postoperative use of the drug.

Some claims have also been made for Vincristin.

CONCLUSIONS

It would appear that emergency surgery and postoperative irradiation to at least the hemiabdomen offer the best hope of cure. Actinomycin D administered during the course of radiotherapy may improve the prognosis further and is now administered routinely in cases with evidence of spread at operation. Local and distant metastases respond well for short periods to both radiation and actinomycin D.

PROGNOSIS

It is observed in most series that the average time from diagnosis to death is one year and that most recurrences or metastases occur within 2-4 months of the initial attack on the disease. It is generally considered, therefore, that if a child survives 2-3 years after initial management without recurrence, he is cured. Collins[4] has defined the period of risk for this tumour more

accurately. His contention is that diagnosis is preceded by a period of silent growth. In a child, this period cannot be longer than 9 months gestation plus the age of the child at diagnosis. If the tumour grows at a characteristic rate, and if one cell is left after initial treatment, this cell would again produce a recognizable tumour in the same period of time: i.e., nine months plus the age of the child. This period is called "the period of risk" and if there is no recurrence during this period, the child should be cured. This rule has never yet been violated. It does not however apply where intermittent chemotherapy which may suppress tumour growth is used.

The following measurable factors are known to influence the prognosis:

1. age is the most important factor in prognosis. Children under 1 year of age are consistently found to have a cure rate twice that of children over 1 year.

2. clincial reaction: The following symptoms occur with spread of the tumour and are generally held to indicate a poor prognosis if present at the outset—hematuria, hypertension, persistant anemia, ascites, cough, bone pain, irritability, anorexia.

3. pathology: encapsulated tumours have a much better prognosis than those that have invaded the capsule or rupture spontaneously or in the course of treatment. No relation of prognosis to histology has been observed.

4. treatment: the prognosis of Wilms tumour has become considerable less gloomy with improved management in the last 2 decades as the following figures from a study by Gross[9] at Children's Hospital in Boston indicate:

CURE RATE

	< 1 year	> 1 year	total
1914-1930	42.8	5.0	14.9
1931-1939	71.4	20.8	37.2
1940-1947	80.0	43.3	47.3

The improvement between 1930 and 1940, Gross attributes to the dramatic drop in operative mortality and the improvement since 1940 to the routine use of post-operative irradiation. 43.3% overall survival is an average figure. Other series record 15-75% 2½ year overall survival, but the trend to decreasing mortality is generalized. These figures may improve further with chemotherapy.

SUMMARY

Wilms tumour is an embryonal mixed tumour of the kidney seen in children under 10 years of age. It arises in the metanephric blastema and may contain undifferentiated cells, abortive renal structures or aberrant mesodermal tissues. It spreads chiefly by the blood stream to lung. The most common mode of presentation is an asymptomatic loin mass, and diagnosis is usually made by intravenous pyelogram. Treatment by nephrectomy, irradiation and chemotherapy has been discussed, and nephrectomy with subsequent radiation to the hemiabdomen is advised. Most recurrences appear within 1½ years of diagnosis, and survival without recurrence for this period usually indicates cure. Survival rate at the present time is about 80% for children under 1 year of age and 40% for those over 1 year of age. In view of the relatively good prognosis of tumours treated before metastases occur, it is important to examine the abdomen of all children seen in routine practice carefully.

ACKNOWLEDGEMENT

Many thanks to Dr. J. M. Darte of the Sick Children's Hospital for his aid in writing this article.

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Recent Advances

Cancer Chemotherapy: Local Infusion Of Antimetabolites

A principal difficulty in the use of drugs for cancer treatment is that agents potent enough to arrest the tumour may be toxic enough to kill the host as well. If the agent is infused into the local artery supplying the neoplasm, a high drug concentration will be present at the tumour site. This enhances the effectiveness of the drug. At the same time, the lower concentration in the general circulation lessens the systemic toxicity.

Currently, antimetabolites such as 5-fluoro-uracil, 5-fluoro-2-deoxyuidine, 6-mercaptopurine, and 4-amino-N^{10}-methyl-pteroylglutamic acid (amethopterin, Methotrexate) are applied by local infusion techniques. Because it is used widely, and because it is used with a systemic antidote, our illustrative example will be Methotrexate. Methotrexate is a competitive inhibitor of the enzyme which converts the vitamin folic acid to the active metabolite folinic acid (citrovorum factor). Folinic acid plays an essential, although not completely known, role in the synthesis of purines and pyrimidines and hence deoxyribosenucleic acid (DNA). Thus, if no folinic acid is present at the tumour site, DNA production, and mitosis of the neoplastic cells cannot occur. Injection of citrovorum factor systemically (intramuscularly) allows the host tissues to receive this essential metabolite and permits the sensitive tissues to reproduce normally. The hazard of giving this antidote is that some will reach the tumour. This small amount of available folinic acid might permit some reproduction of tumour cells. This hazard must be balanced against the severe systemic toxicity of Methotrexate administered without citovorum factor, and the very high local Methotrexate concentration (10-20 times lethal dose) which use of citovorum factor facilitates. However, to be effective, not only must Methotrexate be applied in high concentrations but also it must be given continuously over the period sufficient for *all* the tumour cells to divide. Although this interval varies from tumour to tumour, tissue cultures studies indicate that the order of time required is 6 to 8 weeks.

Now, to use a conventional pump for infusion of a drug at arterial pressure constantly throughout this period is extremely difficult for the patient, not to mention his medical attendants. Watkins has provided a solution for this problem of inventing a portable pump and reservoir, contained in a package the size of a transistor radio. This pump infuses concentrated drug solution at a rate such that the solution may be replaced on an outpatient basis, once every 5-7 days. Thus, with this pump the patient may be ambulant, and, providing that he is well enough, he may lead a conventional albeit restricted life during his treatment.

Correct placement of the catheter is most important, not only to produce the desired high local, low systemic drug concentration, but also to avoid complications relating to the catheter in the artery. Therefore, angiography is often done preceding insertion of the catheter. Then, the catheter (made of teflon and siliconized for minimum tissue reaction) is introduced into the artery. After this has been done, fluorescein solution is injected through the catheter. The arterial distribution of the infusate may be seen dramatically by the fluorescence of the area in the presence of ultra-violet light. If the infusate is not in the optimum area, the catheter's arterial location may be adjusted, and the fluorescein procedure repeated.

Drug infusion is started immediately, or, if the patient is too debilitated, saline is infused until the patient recovers sufficiently to begin therapy.

This technique is most effective with tumours served by one or two arterial branches and with relatively poor collateral circulation. Such areas include tumours of the head and neck, tumours of the extremities, primary carcinoma of the liver or proximal bile ducts (infusion via hepatic artery), pelvic malignancies (infusion via internal iliac artery). Local toxic effects such as skin erythema and mucositis over the tumour site, or a slight chemical hepatitis with liver infusions are indications that the drug is present and active at the intended location.

Frequent serious complications arise from the short or long term insertion of the catheter, and from drug toxicity. Of the former type, displacement of the catheter out of the artery results in leakage of toxic infusion into healthy local tissues, decreased drug concentration at the tumour site, and haemorrhage. A thrombus occluding the catheter's lumen may cause "back-up" and spillage of drug over the patients skin. To prevent this, drug or saline infusion is started at once after the insertion of the catheter. Also, infection or embolus formation may occur around the catheter. Aseptic technique, care in catheter insertion and route of insertion reduce the incidence and severity of these complications. For example, rather than implanting the catheter in the external carotid artery, it is preferrable, where possible, to thread the catheter retrograde via the superior temporal artery.

Drug toxicity of anti-mitotic agents is caused by interrupting the reproduction of normal tissues which divide rapidly. These include, hematopoeitic, lymphoid, gastrointestinal, skin, and gonadal tissues. Complications, severe enough to curtail therapy, are bone marrow depression, haemorrhagic enterocolitis, and increased susceptibility to intercurrent infections.

The response to local infusion therapy varies, and ranges from no improvement, through good palliation (reduction in pain or in size of tumour), partial remissions, to complete cancer regression. Because complete cures at this time are rare, and because of the serious complications of this treatment, local infusion chemotherapy is applied to feasible sites under the following circumstances:

1) cases unsuitable for surgical intervention or radiation therapy, because of location or extent of the mass, or because of previous lack of success with surgery and/or radiotherapy.

2) In selected cases, as a supplement to surgery, radiotherapy, hormonal and other chemotherapeutic measures.

Certainly, as more effective agents become available, and as experience is gained with this technique, the incidence of therapeutic complications will decline. It is equally obvious that advances in this technique will make local infusion chemotherapy play an increasingly important part in the treatment of cancer.

K. Pritzker

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Neuroblastoma

E. P. Braaten 6T6

The neuroblastoma was first described by Virchow in 1864 as a "considerable number" of sympathetic ganglion cells in the adrenal medulla.[4] In 1901 Pepper reported six congenital sarcomas of the right adrenal which spread to the liver and abdominal nodes, and six years later Hutchinson described a number of sarcomas of the left adrenal which metastasized to bone. Subsequently, neuroblastomas were divided into the Pepper and Hutchinson tpyes according to their origin and mode of spread. Farber in 1940 and Karsner in 1942 proved that this division was not justified.

DEFINITION, ORIGIN & CLASSIFICATION

Neuroblastoma is a term used to describe a group of malignant tumours of the sympathetic nervous system which arise from the embryonal sympathetic neuroblast, or sympathogonia, and some of its derivatives.

The sympathogonia originates from the neural crest and migrates ventrally along the anterior spinal segmental nerves to give origin to the cells of the sympathetic ganglia and adrenal medulla. In these locations this cell can differentiate along one of two lines to form a ganglion cell or a paraganglionic cell. The paraganglionic cell can further divide into two cells, a chromaffin cell and a non-chromaffin cell. The chromaffin cell is sometimes called a pheochromocyte because it reduces chromates, a process called the pheochrome reaction.

Tumours of the sympathetic nervous system are usually classified as a subgroup of the tumours of the peripheral nervous system which includes as its other subgroup the tumours of the peripheral nerves, namely, the neuroma, the benign and malignant neurilemmoma, and the benign and malignant neurofibroma.[4] The development and relationship of the neuroblastoma to other tumours of the sympathetic nervous system are represented in the following diagram.

Some authors use the term sympathicoblastoma as synonymous with neuroblastoma;[13] however, in this summary neuroblastoma will refer to all the *malignant* tumours of the precursors of the sympathetic ganglion cell including the sympathogonia. These tumours include the sympathogonio-blastoma, the sympathicoblastoma and the ganglioneuroblastoma. The neuroblastoma of the central nervous system is excluded.

INCIDENCE

Darte[4] found neuroblastomas to represent about 10% of malignancies of infants and children, and to be nearly

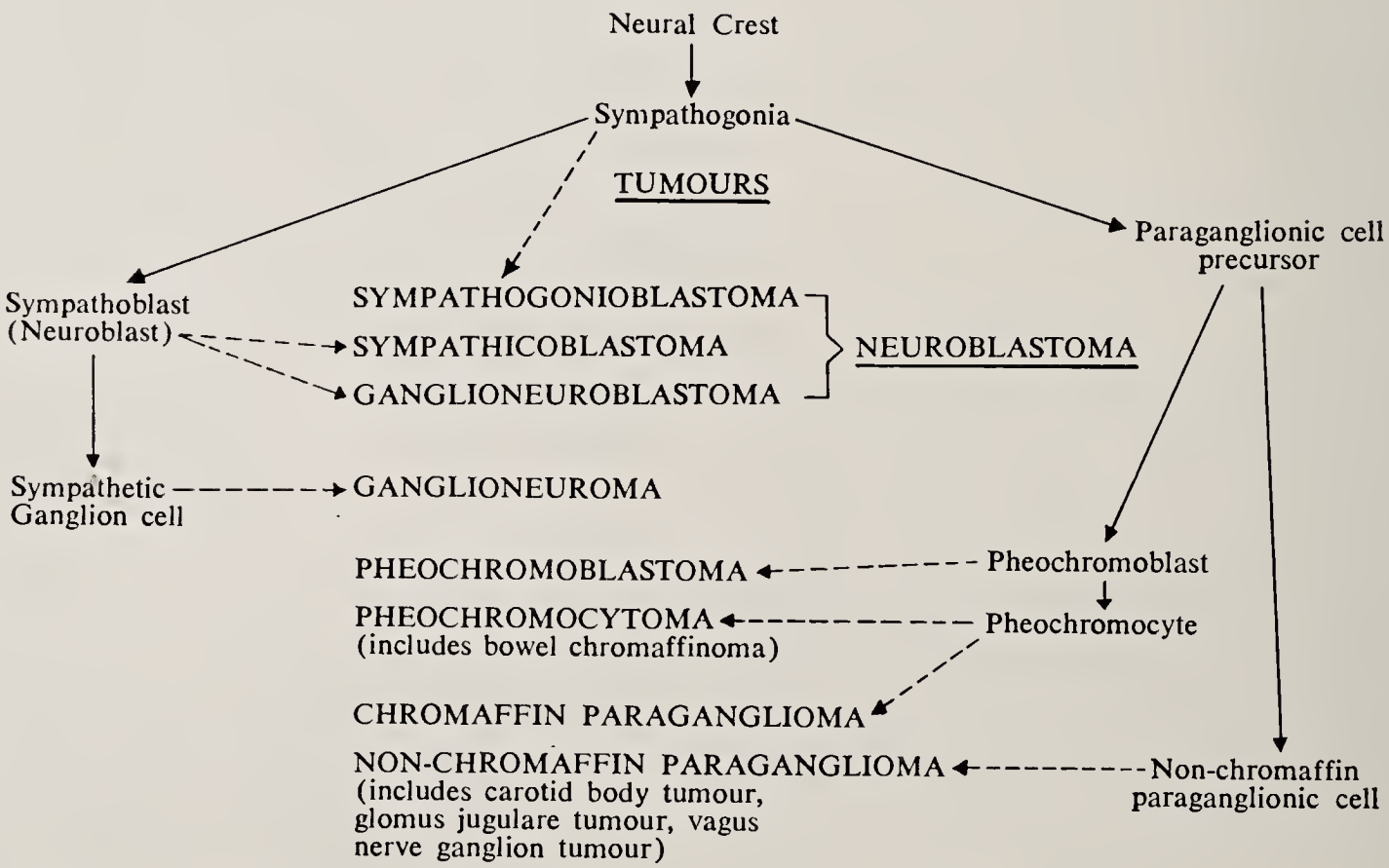

FIG. 1. Classification of the tumours of the Sympathetic Nervous system (in capital letters) according to their cell of origin (in parentheses—see underlined words)

as common as Wilm's tumour. Most studies however found the neuroblastoma to be the most common abdominal neoplasm in this age group.[1 4 9 13] This tumour usually occurs within the first four years of life,[1] but most series report a few cases in adults[4 7 8] Gross et al[7] reported 76% of his patients to be under 5 years of age. In his series about 50% were diagnosed within the first two years of life. Rarely, this tumour may begin in utero, and because of the size of metastases may cause dystocia.[8] It is also reported as an incidental autopsy finding. There is no predilection for either sex.

PATHOLOGY

Gross

The size of a neuroblastoma can vary from a few millimeters to an extremely large mass.[8] Initially, it has a smoothly rounded contour, but becomes finely nodular as the lesion expands. An important feature, which occurs with maturation, is its marked vascularity. The surface is mottled by hemorrhagic areas, and it bleeds freely when cut. It may cut with a gritty sensation if there are foci of calcification,[13] and the cut surface is white with red hemorrhage, brown blood pigment and yellow necrosis. At first the tumour is rather well encapsulated, but later it has a thin limiting membrane which is easily broken as it invades adjacent tissues.

Lymph node metastases are discrete nodular and firm, resembling lymphomata, and liver secondaries are large pinkish nodular masses which sometimes have a pseudocapsule. Bone metastases are lytic in nature, and occasionally have a marked periosteal reaction.

Microscopic

This is a very cellular tumour with a scanty amount of stroma. Often the cells are very immature, and are confused with one of the lymphomas. The malignant cell is round and small, 7-8 microns in diameter, and is arranged with others in broad sheets and clusters, and in many cases definite rosettes can be seen. A large, chromatin-rich nucleus occupies much of the cell. A thin ring of clear cytoplasm surrounds the nucleus, and occasionally, a process of cytoplasm extends out from one side of the cell. The intercellular spaces contain a highly vascular hyalin stroma. In some cases imperfect nerve fibrils are seen connecting groups of neurocytes.[13]

NATURAL HISTORY

Sites

If the migration of the sympathetic neuroblast is understood, the possible sites of a primary neuroblastoma can be readily predicted. The most frequently recorded site is the adrenal medulla. Gross et al[7] found the tumour arising from the adrenal in 40% of cases, the paravertebral region in the thorax in 11%, the retroperitoneal sympathetic chain in 5%, the pelvis in 6%, the neck in 2%, and from unknown origin in about 30%. Similar findings are given in other studies.[5 9 18] Occasionally, primaries arise from other sympathetic nervous tissue including the aortic body and celiac ganglion; rarely the tumour arises in multiple sites simultaneously.

In order to comprehend a primary tumour outside the sympathetic nervous system, one might postulate "the inclusion of primitive ectopic cells in tissues early in fetal life[4]". Aberrant sites include the kidney, liver, skin and subcutaneous tissues.

Development and Spread

Growth may be slow, but it is usually very rapid. It can invade its capsule and spread by direct extension to all contiguous structures. The invasion of vital structures eliminates the possibility of complete surgical removal, and thus lowers the survival rate. In addition, neuroblastomas tend to metastasize early via the blood stream and lymphatics. 60-70% of patients have secondary spread at the time of diagnosis.[7 18] Metastases occur in decreasing order of frequency to bone, regional nodes, liver, skull and orbit, and lungs.[4] Routine chest x-rays, except in the case of neuroblastoma of the mediastinum, are not of much value. On the other hand chest x-rays are ordered routinely in Wilms' tumour, as it usually spreads to the lung within a few months of treatment.

Course of the Disease

Effective surgery and radiation can be expected to cure approximately 35% of all cases. Seven years ago the fatal cases underwent a rapid downhill course followed by death within a few months. Ninety percent of these cases were dead within a year and 99% were dead within two years of the onset of their disease.[7] More recently, it seems that cyclophosphamide has delayed the death and improved the symptoms of previously early fatal cases; however, it has not increased the overall survival.[15]

Spontaneous cures may be expected in a few cases on the basis of maturation of the malignant neuroblastoma into the more benign ganglio-neuroma. Regression of the tumour after some form of trauma, such as hemorrhage into the lesion, was first reported by Farber in 1940.

DIAGNOSIS

Symptoms and Signs

A study of 97 cases at the Hospital for Sick Children in Toronto reported that 35% of complaints were nonspecific and could be related to chronic disease, 30% were related to the primary site, 25% were associated with metastases, and 10% were coincidental. A few had symptoms of diarrhea, sweating and irritability

which were probably due to the tumour secretion of catecholamines.[3]

Some non-specific symptoms are anorexia, general malaise, fever, weight loss and pallor.

Symptoms and signs related to the primary disease depend on location. Abdominal disease may give rise to a mass or general abdominal enlargement, abdominal pain, nausea and vomiting or a change in bowel habits. Mediastinal involvement may cause dyspnea; however, the lesion is usually discovered on a chest x-ray. Neuroblastomas of the pelvis may give rise to urinary complaints or constipation. Cervical disease may produce a Horner's syndrome.

Clinical features of metastatic disease are manifold. Pain, swelling or a fracture may occur with secondaries in the skull or long bones. Cole[3] found hepatomegaly in about 35% of cases. Ecchymosis of the eyelids sometimes precedes exophthalmos in retro-orbital metastases. Paraplegia may present as the result of extradural extension of a paravertebral tumour. Darte[5] found a high incidence of the occurrence of paraplegia with mediastinal neuroblastoma, and, consequently, he performs a myelogram in all cases of mediastinal involvement.

Laboratory Investigation

Until recently specific pre-operative investigation for a suspected neuroblastoma consisted of an intravenous pyelogram, a skeletal survey and a bone marrow aspiration. At present, urinary assays for catecholamines and their metabolites may confirm the diagnosis before operation and biopsy.

Anemia is a common finding. Cole[3] reported an anemia of less than 10 Grams % in 50% of his cases. Leucocytosis and fever may occur and simulate an infection.

Roentgenographic studies are very helpful in assisting in the diagnosis. A flat plate of the abdomen or a chest film may demonstrate a paravertebral calcified mass. An IVP may show a lateral and downward displacement of the kidney and ureter. Pelvo-calyceal distortion is more common in Wilms' tumour, but is occasionally seen in neuroblastoma if the tumour has invaded the renal parenchyma. A metastatic survey may reveal small, multiple, irregular osteolytic lesions in the skull and vertebrae, and/or wedge shape lesions extending from the cortex into the medulla at the distal end of the tubular long bones. Repeat surveys are performed on a followup basis on those patients who originally had metastases to bone in order to check the effects of irradiation.

The *bone marrow* is sometimes involved without x-ray evidence of bony disease. Cells, arranged in a rosette pattern or in clumps, and having large deeply staining nuclei, may be found in the marrow smear.

The findings of *urinary assays for catecholamines* and their *metabolites* are clarified by recalling the metabolism of the neurohormones. Norepinephrine is the principal hormone of the sympathetic nervous system, and is produced by three consecutive enzymatic steps from the essential amino acid tyrosine. The adrenal medulla has a fourth enzyme which converts the majority of norepinephrine to epinephrine (adrenalin). In the body these physiologically active catecholamines and precursors are converted to inert acids; specifically, dopamine is changed to homovanillic acid (HVA) and epinephrine and norepinephrine are converted to vanilmandelic acid (VMA).

Most children with a neuroblastoma excrete increased amounts of HVA and VMA in their urine along with smaller amounts of the pressor amine precursors. Individuals with a pheochromcytoma excrete increased quantities of noradrenaline, adrenaline and VMA, but normal amounts of dopamine and HVA. Williams[20] postulated increased amounts of the enzymes E_1 to E_3 in neuroblastoma and a rise in E_3 and E_4 in pheochromocytoma to account for these results. He thought the benign ganglioneuroma excreted a normal amount of HVA and VMA; however, other studies[14] give evidence to show that the ganglioneuroma has a greater capacity for catecholamine secretion than the neuroblastoma.

Normal urinary values for the acid metabolites VMA and HVA vary according to their method of determination. At the Hospital for Sick Children in Toronto only VMA assays are performed. At this center normal VMA values, attained by a colorimetric method using light of wave length 495Å, range from 80-130 micrograms/kgm. The Association of clinical pathologists[21] found HVA, by chromatographic estimation, to be normally less than

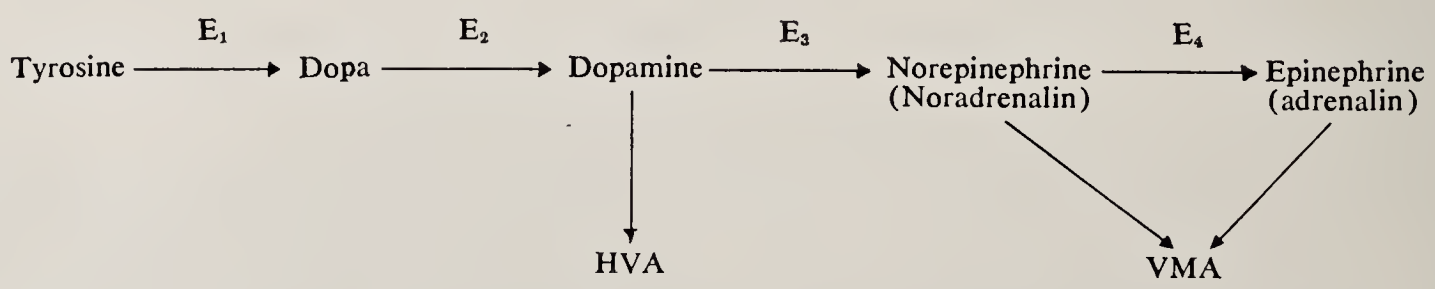

FIG. 2. Production of catecholamines and breakdown products: E_1, E_2, E_3 are found in the SNS and adrenal medulla. E_4 is found in the adrenal medulla alone.

10 mg/24 Hr. A value greater than 15 mg/24 Hr. is suggestive of a dopamine secreting neuroblastoma or ganglioneuroma.

These urinary studies are not only of diagnostic value, but are useful in following the effectiveness of treatment and in predicting the prognosis. For example, a case with an "inoperable neuroblastoma" was described which originated from the right adrenal and was treated with irradiation and chemotherapy.[17] The urinary dopamine and noradrenaline values did not reach normal levels, and consequently an attempt at resection of the mass was then undertaken. Subsequently, the urinary dopamine and noradrenaline levels returned to normal and there was no evidence of recurrence.

Differential Diagnosis

Most pediatric neoplasms are diagnosed late and the neuroblastoma is no exception. Two-thirds of cases show disseminated disease when first seen.[1] Approximately 50% are incorrectly diagnosed initially.[3 11] Abdominal swelling is commonly misinterpreted as Wilms' tumour. Fever, anemia and bone pain lead one to suspect rheumatic fever.[11] IVP changes are incorrectly diagnosed as Wilms' tumour, hydronephrosis, or retroperitoneal lymphoma. Lesions found in bone surveys are mistaken to be leukemia, Ewing's sarcoma, reticuloendothelioses, tuberculosis or Hand-Schuller-Christian disease. The skull x-ray with its bony trabeculation with spicules arranged vertically is incorrectly called a meningioma, osteogenic sarcoma, sickle cell anemia or thalassemia.[8] The microscopic appearance of an anaplastic tumour is often confused with lymphosarcoma, rhabdomyosarcoma or Ewing's sarcoma.

TREATMENT AND RESULTS

The most commonly accepted treatment for a *localized* primary neuroblastoma is the excision of as much tumour as is surgically possible followed by irradiation to the tumour bed. Most series report approximately 60% cure with this regimen.[5 7 9 17] In 24 of his patients, Gross et al[7] showed that the survival rate could be increased to 88% if the tumour was totally excised.

It seems that the removal of a part of the tumour even in the presence of metastases is better than biopsy alone.[9] Dargeon[4] suggested that this may be due to the resection of the most malignant of a group of tumours of multicentric origin and/or the depression of a physiological reciprocal growth of tumour cells in various parts of the body. Koop[9] discovered that the contamination of the abdominal cavity at operation with neuroblastoma cells did not alter the final prognosis. This is not true of Wilms' tumour.

The benefit of radiotherapy as an adjunct to surgery is still questioned. In a series of 100 patients treated by Koop[11] only 13 of 31 survivors had post-operative irradiation. In addition in a previous series Koop had a higher mortality rate with surgery and irradiation than with surgery alone. Most centers, however, irradiate the tumour bed. Darte[5] achieved as high a survival rate in abdominal tumours with or without metastases to the liver. He treats the whole abdomen including the liver with 2000-2200 rads (1200-1500 rads in children under 1 year) taking care to shield the hip joint, and the kidney on the contralateral side.

The treatment of *disseminated* disease depends on the site and extent of spread. Liver and solitary bone metastases are treated with a radical dose of irradiation, about 2000 rads. Patients with multiple secondaries to bone and/or retro-orbital area are given palliative irradiation, about 500-1000 rads, or chemotherapy. Liver metastases can be successfully irradiated in about 60% of cases; however, patients with multiple bone metastases and/or bone marrow involvement rarely survive.

A few cancer chemotherapeutic agents have given effective palliative relief, but there are no figures which would suggest that any agent significantly increases the overall survival. Cyclophosphamide (Procytox) is the agent of choice at the Hospital for Sick Children in Toronto;[15] other alkylating agents, amethopterin, and Actinomycin D have been tried with little effect. Bodian[1] felt that Vitamin B_{12} markedly decreased the growth rate of the neuroblastoma; however, other investigators have failed to verify his view.

SUMMARY OF PROGNOSIS

When considering prognosis one must consider that, in children, a 14 month survival following treatment is equivalent to a 5 year survival in adults.[10] The overall cure rate is about 35% including a few spontaneous cures; however, with localized disease a survival rate of 60% can be achieved with excision of as much tumour as possbile and post-operative irradiation. An 88% cure rate was reported in 24 cases whose lesions were totally excised.

Factors Affecting Prognosis

The *age* of the patient when treated and the *location of the primary and secondary lesions* are all related to the survival. The sooner in life the disease is treated the more favourable the result. Cole[3] found a 70% survival in those children who were treated in the first year of life, a 44% survival in those who were treated in the second year of life, and a 8% survival in those who were treated in the third to fifth years of life. Mediastinal primaries seem to have a better prognosis than abdominal tumours perhaps because they are detected sooner. Cole[3] reported a 42% cure rate in mediastinal primaries and a 28% survival in abdominal neuroblastomas. The last factor affecting prognosis is the site of the secondary lesion. Metastases to the liver don't seem to alter appreciably the survival rate;[5] however,

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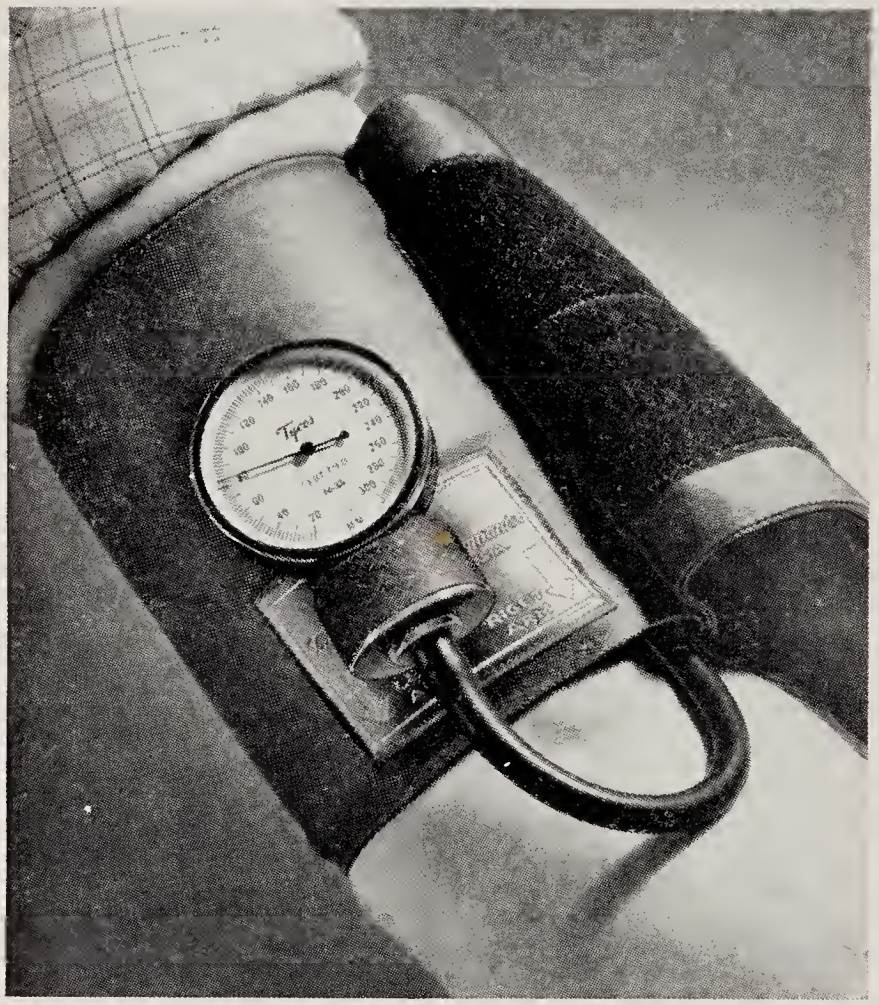

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ACKNOWLEDGEMENT

The author would like to thank Dr. A. R. C. Cole and Dr. M. Sonley for their assistance in the preparation of this article.

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Abstract

The Management of Tiredness

D. B. Coates, M.D., F.R..CP.(C): Applied Ther., Vol. 6, No. 11, November 1964, pp. 916 - 919.

The majority of patients complaining of fatigue alone, do not have an associated specific condition, either physical or emotional. When a specific diagnosis is made, fatigue is usually incidental to more dramatic symptoms. This discussion is limited to the patient whose complaint is fatigue, unaccompanied by other more specific symptoms.

The patient's complaint, considered simply, is an expression of dissatisfaction with the discrepancy between the patient as he seems himself and the way he feels he should be.

Those biological needs which are not, of necessity, quickly satisfied, and which permit a homeostatic lag, easily become invested with a web of personal elaboration or fantasy. Thus, sleep often acquires a prominent psychological component, whereas breathing does not. We rarely achieve true biological fatigue, but often feel tired because of self-imposed limits of habit (diurnal cycle).

Regardless of the exact technic, the elucidation of the symptom is a shared activity of the doctor and patient. Examination may proceed as follows:

(a) Amplify the patient's complaint and exclude any specific diagnosis. Avoid characterization of the problem as "organic" or "experiential". Under careful questioning, the patient's use of emotional words to describe his fatigue can establish the meaning of the symptom.

(b) Other areas of activity may be colored by the same attitude which produce the fatigue. Related symptomatic behavior should be explored.

(c) Having established the meaning of the tiredness, it can be further personalized, and its predominant emotional tone simplified and characterized in the patient's own words.

(d) It is frequently possible to relate the tiredness to a significant relationship e.g. employer, wife, mother-in-law.

After a careful physical examination the patient should be reassured that he has no organic disease. The emphasis in psychiatry on uncovering unconscious meanings can lead to gross misunderstanding in minor psychosomatic disorders. Most patients with these problems give clear hints as to the cause of their symptoms. The reasons for tiredness are usually known to the patients but poorly accepted by them. A good doctor-patient relationship can initiate the necessary relearning. Even when a patient expresses acceptance of his problem, the doctor should expect a lag in results. Through further interviews the physician can give support without recourse to unnecessary advice (of which the patient has had plenty) or non-specific medication. Specific advice to avoid is the recommendation of more rest.

M.L.S.

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Bone Tumours In Children

J. M. Nelems 6T6

The overall incidence of primary bone tumours is small compared with carcinomas of lung, stomach, breast, cervix, thyroid etc. However in patients under twenty years of age, primary bone tumours, with the exception of the leukemias and the lymphomas, constitute the most important single group of malignancies. Therefore in dealing with this age group a working knowledge of bone tumours in general is necessary, because a differential diagnosis will arise in nearly all cases involving one or more bone lesions.

Any patient presenting with clinical signs and symptoms suggestive of a bone tumour should be investigated as quickly and thoroughly as is expedient for both patient and physician. The reason for this is that a malignant bone tumour may have to be treated radically, often requiring amputation of a limb, or wide excision of an involved area. It is extremely important therefore to differentiate a malignant lesion from a benign or non-neoplastic lesion.

APPROACH TO DIAGNOSIS

History of Presenting Symptoms

Disability varies greatly depending on the site and extent of the lesion. A limp is one of the earliest symptoms if the lesion is in the lower extremities. Pathological fracture is likewise common.

Pain is another early symptom of a malignant bone tumour. Initially it is mild, and often intermittent. Its onset is insidious. Soon, however the pain becomes progressively more severe, but rarely excruciating. It is often worse at night, and is usually experienced at or near the site of the lesion. Not infrequently however, the pain may be referred to an area distant from the lesion. This is commonly the case with tumours about the hip in which the pain is referred to the knee. With this symptom alone, one should suspect bone sarcoma and progress with the necessary investigations to rule out this possibility.

Swelling is usually noted after the pain has been present for some time. It is more easily recognized in bones sparsely covered by tissues than in those more deeply seated, such as the pelvic bones, or the neck of femur.

A history of very minimal chronic fatigue, of anorexia, and of loss of normal childhood vitality is of great importance where a malignant bone tumour exists.

Superficial varicosities are noted when tumour obstructs the local venous drainage.

History of Past Health

Of particular note here is a history of those illnesses that may give rise to bone lesions such as osteomyelitis, tuberculosis, syphilis, trauma, previous fractures and any form of malignant disease.

Physical Examination

Inspection may reveal a limp, local swelling and heat, discoloration of the skin, dilatation of the superficial veins, and frequently the deformity of a pathological fracture.

Palpation of the tumour may indicate its extent and consistency. Tenderness is an important and frequent finding with malignant lesions. Rapidly growing tumours may not be bony hard but more often rubbery and elastic. The skin is usually not attached to the underlying tumour. Varicosities distal to the area of involvement are a poor prognostic sign indicating invasion and blockage of the veins. Lymphadenitis is rare, simply because primary bone tumours only infrequently spread via the lymphatics. Pulsation is equally uncommon.

Radiological Examination

With the exception of histological examination, the X-ray apperance of a bony lesion is perhaps the most valuable step in the diagnostic survey of bone tumours. It shows the location of the lesion with respect to the bone as a whole, the destruction and involvement of the original osseous tissue at the site of the tumour, the response which the lesion may provoke in the adjacent bone and periosteum, and the X-ray characteristics of the lesion itself. The X-ray itself, without the clinical findings, seldom gives one the specific definitive diagnosis.

Chest films as well as a skeletal survey should be done routinely on all patients with suspected bone tumours.

Laboratory Investigation

In interpreting laboratory results it is well to remember the level of alkaline phosphatase, the index of osteoblast proliferation, may be up to in normal children. Calcium and inorganic phosphate have an upper limit of normal of 12 mgms/100ml and 6 mgms/100ml.

The following laboratory investigations are a helpful adjunct in making a definitive diagnosis: complete blood count including Hbg., WBC, smear with differential and ESR; alkaline phosphatase; serum calcium and inorganic phosphate; serum proteins and protein fractions. Perhaps the most helpful single index of a malignant

bone tumour is an elevated ESR. The ESR is also one of the most useful tests to follow the results of treatment of a malignant lesion.

Biopsy

A biopsy is considered as the final step in the diagnostic survey, and in most instances it is mandatory. If a lesion is not biopsied because it is thought to be benign, then it must be followed up with periodic check X-rays. Once the decision to proceed with the biopsy has been made, the technique of biopsy has then to be chosen. Needle biopsy is simple, but usually provides small and inadequate tissue specimens. Therefore open surgical biopsy is preferred. If the lesion is not too large, an excisional biopsy may be done.

The intepretation of bone biopsies presents some unique problems. Bone, being hard, is a difficult tissue to prepare for quick section. Nevertheless, even with adequate preparations, the histological diagnosis may also be difficult, since similar classes of tumours may look very different. The degree of anaplasia is not always an accurate guide to the clinical behaviorism of a bone tumour. A wild looking mass of myositis ossificans will have no tendency to metastasize, while a benign looking giant cell tumour may spread rapidly with distant metastases.

DIFFERENTIAL DIAGNOSIS OF A BONE TUMOUR IN CHILDREN

In most cases of bone tumours, a conclusive diagnosis can be made by means of an adequate investigation. In some cases however, it may be difficult to distinguish the forms of primary bone malignancies from each other, from benign bone tumours, and from certain non-neoplastic bone conditions.

While some bone neoplasms occur at any age, others are far more common in the earlier years of life, and it is these conditions that shall be briefly considered.

Fibrous Cortical Defect

This common, self-limiting condition is a benign bony defect composed of fibrous tissue with varying degrees of cellularity. It affects males twice as often as females. It occurs most frequently in the first 8 years of life, but rarely after age 15. Fibrous tissue develops out of the local periosteum, and invades the underlying bony cortex, most commonly near the epiphyseal plates of long cylindical bones. The deep and advancing edge of the lesion may reveal a limiting zone of sclerosis, while the overlying periosteum may produce a thin layer of bone roofing the cortical defect. They are usually asymptomatic, and heal spontaneously in 2-3 years. Very occasionally they may persist and undergo proliferative activity. They are then known as non-ossfiying fibromas of bone.

Solitary Bone Cyst

This lesion is comprised of a cyst cavity filled with a straw coloured or blood tinged fluid. It too affects males twice as often as females. Its greatest incidence is in the first 8-10 years of life. These bone cysts are usually found in the metaphyses of long bones. They are most commonly asymptomatic until pathological fracture occurs. Radiologically they appear to be relatively large radiolucent centrally located lesions, with scattered fibrous trabeculae. The cortex is usually thinned, the bony contour slightly expanded, and the periosteum smooth. No evidence of new bone formation will be found. More than 50% of these cysts occur in the proximal metaphysis of the humerus. They are also commonly seen in the neck of the femur.

The treatment of choice is to explore the cyst, curet its walls, fill the defect with autogenous bone chips, and close the wound tightly.

Aneurysmal Bone Cyst

This blood filled cyst gets its name not because of its resemblance to a true aneurysm, but because radiologically the contour of the outer margin of the lesion is bulging and distended. The cortex beneath the cyst is usually thinned or partly disintegrated.

It is a relatively rare condition with a peak incidence among adolescents.

Osteoid Osteoma

Osteoid osteoma is a peculiar benign tumour of osteoblastic derivation. It is a small round tumour consisting of an osteoid nidus with trabeculae of newly formed bone deposited within the matrix of highly vascularized osteogenic connective tissue. The nidus is usually surrounded by a zone of reactive sclerosis. It is unusual in that it rarely exceeds one centimeter in diameter. It may develop in the cortex of an affected bone, or within the spongiosa, frequently near an articular surface. There is a predilection for the femur and tibia. On X-ray the nidus shows as a characteristically radiolucent focus in the affected bone surrounded by a reactive zone of sclerosis.

The diagnosis is relatively simple in most cases. It is found mainly in older children, adolescents and young adults. Males are affected more frequently than females. The presenting symptoms are a constant low grade pain typically relieved by aspirin, and localized tenderness. A limp is often observed early on in the course of the lesion.

Surgical excision usually brings immediate and dramatic relief from the symptoms.

Solitary and Multiple Osteocartilaginous Exostoses

Both solitary and multiple osteocartilaginous exostoses are cartilage-capped bony projections arising in

the metaphysial area of bones from their cortical surfaces.

Solitary exostosis is the commonest of the primary benign skeletal neoplasms. Most patients presenting with these lesions are children and young adults. There is no sex difference. They are usually asymptomatic, but on occasion they produce signs and symptoms related to pressure on adjacent tissues. The great majority are confined to the distal end of the femur, and the proximal ends of the tibia and fibula. Radiologically, these can be diagnosed with ease as the contour of the exostosis is sharply delineated. The consistency of the lesion is not unlike that of normal bone.

Multiple exostoses are characterized by the presence of wide spread skeletal bony protrusions. This is a rare hereditary condition. When severe, the disorder may be manifest in nearly all bones preformed in cartilage. The lesions tend to be bilateral and symmetrical in distribution. Of particular note regarding multiple exostoses is the fact that about 10% of patients will sooner or later have malignant chondrosarcomatous degeneration in one or more of the exostoses. Less than 1% of solitary exostoses will become malignant.

Treatment by surgical excision is therefore directed against all cases that undergo malignant change or produce clinical symptoms.

Solitary Enchondroma and Multiple Enchondromatosis

These conditions are benign cartilaginous neoplasms arising in the medullary cavity of bone.

Solitary enchondroma is a fairly common lesion found mainly in both long and short tubular bones of the limbs. The phalanges of the fingers and the metacarpal bones are most frequently affected. The lesion is eccentrically located, enlarges the medullary cavity, thins the adjacent cortex, and distends the overlying periosteum. Radiologically, the lesion appears as a round to oval area of rarefaction confined to the shaft of the bone. This disease is encountered most often between the ages of 10-30. Local swelling is the commonest clinical complaint. Pain is rarely associated with this lesion unless there is a concommitant pathological fracture.

Multiple enchondromatosis is a rare non-hereditary condition. Essentially the lesions are similar to the solitary enchondroma but with involvement of many bones.

Chondrosarcoma has been reported to develop in about 50% of patients with multiple enchondromatosis, and only in 1% of patients with a single lesion. Surgical excision is indicated in all cases with suspected malignant change, and in cases producing clinical symptoms or gross deformity.

Osteogenic Sarcoma

Osteogenic sarcoma is defined as a malignant neoplasm which forms osteoid and osseous tissue in the course of its development. It is the commonest of the primary bone malignancies, with a peak incidence in the second decade of life. It occurs occasionally under age 10, but very rarely under age 5. Affected males outnumber females by 2:1. This sarcoma seems to have a predilection for the metaphyseal ends of long bones where rapid growth changes are occuring. The distal end of the femur and the proximal end of the tibia account for more than 50% of all cases.

Clinically these patients will present with all the signs and symptoms of a malignant bone lesion as outlined earlier. In children, a limp is usually the first suspicion of malignant activity. Lethargy, anorexia, and general disinterest, although non-specific and minimal at first, frequently precede pain and obvious swelling. Careful attention should therefore be paid to such findings. An elevated ESR and alkaline phosphatase are the only significant blood changes.

The X-ray appearance of osteogenic sarcoma is extremely variable. In about 50% of cases the findings are quite characteristic; the tumour having perforated the cortex and invaded the surrounding tissue. There are large areas of radiopacity within the tumour mass due to the extensive ossification and calcification. On occasions there may be conspicuous perpendicular striations of new bone within the subperiosteal tumour cuff. This striated appearance, however, is not specific for osteogenic sarcoma. It may also be seen in the Ewing's sarcoma, with metastatic carcinoma or with myositis ossificans. With elevation of the periosteum there may be a small amount of reactive new bone deposited on either side of the lesion, known as Codman's triangle. In approximately another 30% of cases, the features just described will be present, but very much less apparent. In the remaining cases the osseous activity of the tumour may not be striking, the mass may not be extensive, and diagnosis rests upon microscopic interpretation.

Radical surgical amputation or disarticulation is the treatment of choice in an accessible site. Being a moderately radiosensitive tumour, an alternate method of therapy is to give pre-operative radiation. If, after 3 months, there are no chest secondaries on X-ray, surgical amputation is then performed. Despite the most vigorous treatment however, the overall prognosis for osteogenic sarcoma is very poor. Five year survival figures are variously quoted between 10-20%. It seems that lesions in the head and neck, the trunk, the proximal femur and the proximal humerus are almost all fatal. The chances of survival improve somewhat when the tumour arises at points more distal from the trunk. Five-year survival figures for the distal shaft of femur and the proximal shaft of tibia are quoted as 17% and 34% respectively.

Ewing's Sarcoma

There has been much controversy regarding Ewing's sarcoma. In 1921 Ewing first described this sarcoma as a separate tumour arising de novo in bone from endo-

thelial tissue. Lichtenstein has also suggested the reticulum cell or primitive connective tissue cell as a possible source of genesis. Let it be defined then as a rare malignant tumour arising in the marrow portion of bone.

Like osteogenic sarcoma, Ewing's sarcoma has a peak incidence in the second decade of life. It is, however, much rarer than osteogenic sarcoma. Ewing's sarcoma almost never occurs before age 5. This is a useful observation in its differentiation from neuroblastoma secondarily in bone, since most cases of neuroblastoma occur before age 5. The pelvis and the long limb bones are most frequently involved.

Patients with Ewing's sarcoma usually have the typical findings associated with a malignant bone lesion. Pain, limp, swelling, and anorexia are of importance, but of particular note is an elevated ESR, with leukocytosis, fever, anemia, and local heat. It has a peculiar tendency to metastasize to other bones, so much so that some people consider this lesion to be multicentric in origin.

This disease induces bone lysis, and since it has no osteogenic potentiality, the X-ray appearance is that of an area of mottled rarefaction. Evidence of rapid extension through the bone and into the surrounding soft tissue is usually apparent as well. Later on in the development of the lesion, the rarefaction may give way to a radiopacity due to reactive bone formation at the level of the tumour. If there is extensive involvement of a shaft, there is often an associated "onion-skin-like" periosteal reactive new bone formation.

Radiation therapy is at present the treatment of choice. A total dose of 5000 r is delivered through multiple portals, and fractionated at a rate of 300 r/day. This seems to control the primary lesion and relieve the symptoms, but almost invariably the sarcoma will either reappear locally or at some distant point. The overall prognosis is very poor indeed with a 5 year survival rate of 0 - 3%.

Childhood Tumours Metastatic to the Skeleton

While the leukemias, the lymphomas and neuroblastoma have been dealt with in detail elsewhere in this journal, it should be recalled here that patients will frequently present for the first time with skeletal manifestations of these diseases.

Histiocytosis — X

This category includes the spectrum of conditions ranging from the usually solitary eosinophilic granuloma to the rapidly fatal and widespread Letterer-Siwe disease. The Hans-Schuller-Christian syndrome lies somewhere between these two extremes. Histiocytosis —X is included in this differential diagnosis because bone lesions dominate its pathology.

These lesions may occur in any bone but most frequently they are found in the skull and long bones. They are painful and sometimes expansile. Radiologically they appear as discretely defined defects. There may be some periosteal reaction if the cortex is eroded or when pathological fracture has occured.

Cutaneous manifestations, lymphadenopathy, and hepato-splenomegaly frequently accompany the bone lesions of the more fatal end of the spectrum.

Myositis Ossificans and Osteomyelitis

These non-neoplastic conditions mimic malignant growths of bone so closely that their importance can not be overemphasized.

Myositis ossificans is commonly mistaken for osteogenic sarcoma. However, unlike osteogenic sarcoma it is nearly always associated with a history of antecedent local trauma. If the part is easily accessible to palpation, a local painful soft tissue swelling will soon be felt. It grows in size more rapidly than a sarcoma of bone, reaching a maximum size in about two months. Unlike a malignant lesion, myositis ossificans presents a well circumscribed mass that may or may not impinge on adjacent bone. It compresses rather than infiltrates the surrounding tissue.

Acute osteomyelitis and Ewing's sarcoma are quite similar in their clinical appearance. Both are essentially diseases of childhood and adolescence. Both cause limping, local heat, tenderness, fever, leukocytosis and an elevated ESR. One is a treatable disease, the other virtually incurable. The commonest sites of localization of osteomyelitis are the metaphyses of long tubular bones. These areas are very richly vascularized. Any bloodborne bacteria tend to retard the blood flow in the subepiphyseal loop capillaries allowing infection to supervene. The inflammatory reaction penetrates the cortex and lifts the periosteum, thereby stimulating osteoblasts to lay down a reactive involucrum of subperiosteal bone.

In conclusion, the writer would like to thank Dr. W. P. Bobechko for his advice, his constructive criticism, and his enthusiastic support in the writing of this article.

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Lymphomas in Children

S. Lofsky 6TG

The lymphomas comprise those tumours which originate in and are initially localized to lymphoid tissue. They are the fifth most common childhood malignancy, following the leukemias, brain tumours, Wilms tumour, and neuroblastoma in incidence, comprising about 10% of all these tumours. They do not have their maximum incidence in childhood but are most common in adults.

There are two major groupings, Hodgkin's disease and lymphosarcoma. One of the most important differences between these two groupings lies in their means of spread from the primary site. It is generally believed that Hodgkin's disease spreads along lymphatics, so that new disease is commonly found in adjoining lymph nodes, whereas secondaries in lymphosarcoma can appear anywhere in the body. Thus while localized lymphomas of both types can possibly be cured, lymphosarcoma which has spread to nearby areas has likely spread to distant areas also. This is not so often the case in Hodgkin's disease.

HODGKIN'S DISEASE

Hodgkin's disease comprises about 3% of childhood malignancies.[1] The peak age of incidence of Hodgkin's disease in children is reported to be six. Most cases occur between five and nine and the disease is very rare before the age of two years. The ratio of males to females is 3:1.[2]

There are three pathological forms of Hodgkin's disease, the paragranuloma, the granuloma, and the sarcoma. The granuloma, makes up 80% of Hodgkin's disease, the other two forms each making up 10%. The microscopic picture of Hodgkin's disease is characterized by the diagnostic Reed Sternberg cells. The histology of the three different forms varies from the monotonous field of lymphocytes in the benign appearing paragranuloma, and the picture of cellular pleomorphism in the granuloma, to the homogeneous field of hypertrophied reticulum cells in the most malignant appearing sarcoma. Grossly the nodes are enlarged, impinging upon, and in the case of the sarcoma, invading nearby structures.

Although the pathology is useful in assessing the degree of malignancy of Hodgkin's disease, the assessment of prognosis appears to be related mainly to clinical staging. The classification of Peters' and Middlemiss'[3] is widely used in determining the type of treatment and in predicting the prognosis:

STAGE I — Involvement of a singie site or lymphatic region.

STAGE II — Involvement of 2 or 3 proximal lymphatic regions.

A. With no symptoms of generalized disease.

B. With symptoms of generalized disease.

STAGE III — Involvement of 2 or more distant lymphatic regions.

Further amplification of clinical staging is necessary. Stage I is self-explanatory, whereas stage II is usually taken to mean disease limited to the upper or lower half of the body by the diaphragm, and stage III disease pertains to disease existing above and below the diaphragm. Splenic or hepatic involvement automatically places the patient in stage III, as does disease demonstrated in the bone marrow, the bones themselves, the pulmonary parenchyma, secondarily in the GI tract, and in two or more cutaneous or subcutaneous areas.[4] Systemic symptoms are very significant as they almost always signify generalized disease.

CLINICAL PICTURE

The clinical picture of Hodgkin's disease in children is similar to that seen in young adults. The most common presentation is that of painless swelling of one or more groups of superficial lymph nodes. The commonest site is the cervical region where the swelling is usually unilateral. Other nodal regions often primarily involved are the axilla, the inguinal region, the para-aortic region and the mediastinum. The involved nodes are usually discrete, fairly firm, nontender, and elastic. Extranodal sites of primary involvement are not common. The enlarging nodes may cause localized manifestations, such as dyspnea, dysphagia, cough and hoarseness because of mediastinal lymphadenopathy, engorgement of the neck vessels and edema due to cervical disease, and ascites and jaundice due to abdominal node involvement. Splenomegaly and hepatomegaly occur very commonly in later stages of Hodgkin's disease.

Occasionally, constitutional symtoms such as fatigue, pruritus, anorexia, weight loss, and a fluctuating fever are the first manifestations. The characteristic and also uncommon Pel-Ebstein fever, consists of periods of one or two weeks of high fever followed by periods of reduced temperature.

Although there are some haematological changes in Hodgkin's disease, they are not specific and are of little significance in the diagnosis.

DIAGNOSIS

The diagnosis is established by biopsy of an involved node. Dissemination of the disease may be

assessed by means of chest x-ray, flat plate of the abdomen, intravenous pyelography, venacavography and lymphangiography, a new technique which outlines the lymphatics and lymph nodes by means of intralymphatic injection of a radiopaque dye.[5] Other tests useful in the investigation of Hodgkin's disease include a complete blood workup, occult blood in the stool, urinalysis, liver and kidney tests, and a marrow biopsy.

Prognosis and Treatment

Overall five year survivals in children with Hodgkin's of 27%[2] and 43%[6] have recently been recorded and these compare favourably with 31%[7] for all ages. The prognosis of individual cases however will depend on clinical staging and the adequacy of treatment. In one series there was a 60% 5 year survival for stage I, and an 18% survival for stage II, with no patients with stage III disease living beyond 3 years. Of this series,[2] 17% are still alive 5 to 33 years after biopsy and thus a cure is possible, a fact in conflict with the widely held notion that the disease, particularly in children, is invariably fatal and progressive. Thus in early Hodgkin's disease the plan of attack must be that of curing the disease rather than an attempt at palliation. In widespread disease the main aims of therapy are to suppress disease activity and to produce long remissions, since a reasonable hope for a cure is unlikely.

a) *Localized disease.* High doses of irradiation to the area of involvement is the treatment of choice in localized (Stage I and IIa) Hodgkin's disease. Peters and Middlemiss have shown in a retrospective study that prophylactic radiation to contiguous clinically uninvolved nodes improved the survival rate 10 to 14%.[8]

Surgery has been recommended by some for the primary treatment of localized Hodgkin's disease. However, it appears that the prognosis of surgery is no better than that of irradiation and that many surgical patients suffer frequent recurrences that later require radiation. However, the treatment of choice for localized Hodgkin's disease of extranodal sites such as the gut, salivary glands, or extradural involvement may be radical surgery with irradiation to the immediate lymphatic drainage.

Chemotherapy has little place in the control of early Hodgkin's disease.

b) *Advanced Disease.* The mainstay of treatment in advanced Hodgkin's disease is palliative chemotherapy. the drug most widely used being nitrogen mustard (HN_2, mechlorethamine), an alkylating agent. In 80% of patients a course of HN_2 will lead to control of fever and subjective symptoms as well as some decrease in tumour size. Treatment should be accompanied by sedation and antiemetics to control nausea and vomiting. Nitrogen mustard may be readministered if necessary after 6 to 8 weeks, though the remissions are usually shorter and less complete. In addition to its use in controlling systemic manifestations and disease beyond the scope of irradiation, nitrogen mustard is used in emergencies such as compression of the vital organs. Radiation following chemotherapy in these situations has been found to be as effective as combined surgery and radiation. Patients with mild constitutional symptoms may frequently be started on chlorambucil (Leukeran), another alkylating agent. This drug can be given orally and is less toxic than HN_2, but its action is slower (3-4 weeks).

Other drugs available are used when alkylating agents have failed to produce a satisfactory remission or have lost their effect through repeated action. Vinkaleukoblastine (Vinblastine sulphate, Velbe, VLB) will produce an objective response lasting two months of more in 50% of patients. Vincristine (Oncovin), a drug related to VLB, is newer and has a high neuromuscular toxicity. Its main use is in cases of therapeutic failure with VLB. A new drug, methyhydrazine, has been shown to be effective in Hodgkin's disease refractory to nitrogen mustard. The use of corticosteroids in Hodgkin's disease is limited mainly to severe hemolytic anemia.

Chemotherapy is most useful in advanced symptomatic disease, but irradiation is important in the management of advanced disease where large tumour masses produce the greatest difficulty. Examples of situations where irradiation is used are obstruction of the airway, oesophagus, bowel, ureters and superior vena cava, and compression of the spinal cord. In these cases chemotherapy should also be used for control of any constitutional manifestations of disease.

LYMPHOSARCOMA

Lymphosarcoma accounts for 3.5% to 7.2% of childhood neoplasms. A recent compilation[9] of 221 cases of childhood lymphosarcoma in the literature has shown a slightly higher incidence at ages 3 to 5 and 9 to 11 years. The male-female ratio is found to be 2.6:1.

The term lymphosarcoma embraces three types of lymphoma: 1) giant follicle lymphoma, 2) reticulum cell sarcoma, 3) and lymphocytic and lymphoblastic lymphosarcoma.

Giant follicle lymphoma is very rare in children, making up only about 3%[10] of lymphosarcoma. Microscopically it consists of giant follicles replacing the normal nodal architecture, and is easily confused with benign reactive hyperplesia. Invasion of the capsule and surrounding tissue is a late feature. Its course follows quite closely that seen in adults and it carries the best prognosis.

Reticulum cell sarcoma accounts for about 16%[9] of lymphosarcoma in children. It is characterized by the replacement of the normal architecture by cells more than twice the diameter[11] of a normal lymphocyte. Invasion of the capsule and surrounding structures is common, accounting for the tendency of the nodes to

become fixed to adjacent tissues and for fusion of involved nodes into solid tumour masses to occur.

Lymphocytic and lymphoblastic lymphosarcoma comprise 82% of the childhood lymphosarcomas. The tumour consists of closely packed lymphoid cells having a diameter of less than twice that of a normal lymphocyte[11], obliterating the structure of the node and extending into or beyond the capsule. Lymphocytic lymphosarcoma describes a type in which the cells resemble small lymphocytes, and lymphoblastic lymphosarcoma describes a type which consists of cells resembling lymphoblasts.

Clear differentiation of one type from another is not always possible. For example, one often finds follicle formation in a node for the most part resembling lymphocytic lymphosarcoma. In addition the picture is further complicated by transitions from one form to another. Giant follicle lymphoma can change to lymphocytic and lymphoblastic lymphosarcoma, lymphocytic lymphosarcoma can change to lymphoblastic lymphosarcoma, and all can go on to an acute leukemia.

Clinical staging is also used in lymphosarcoma and as in Hodgkin's disease it provide a guide to prognosis and treatment:[12]

STAGE I — Involvement of a single lymph node region or a single site in extranodal tissue.

STAGE II — Involvement of multiple lymph node regions or of a single extranodal site, with involvement of an adjacent lymphatic region.

STAGE III — Evidence of systemic disease or involvement of liver, spleen, or bone marrow or single extranodal site with involvement of remote lymphatic regions.

CLINICAL PICTURE

The most common initial manifestation is enlargement of the peripheral nodes, most commonly the cervical nodes. Abdominal symptoms due to involvement of the gastrointestinal tract, retroperitoneal nodes, and other viscera are the second[9 10] most common manifestation. Other, common primary sites include the mediastinum, the nasopharynx, the tonsil, the bones, and the parotid gland. Less commonly the skin, prostate, testes, the eyes, and the CNS are primarily involved. The symptoms and signs produced by the lesions of lymphosarcoma are similar to those produced by Hodgkin's disease in similar areas.

With progression of the disease, there is widespread involvement of lymphoid tissue throughout the body, no organ being immune. Systemic symptoms such as fever, anorexia, and cachexia usually occur in a later phase of disease than in Hodgkin's disease.

Of great importance in the course of lymphosarcoma is the invasion of the bone marrow by lymphosarcoma cells, resulting in an acute lymphocytic leukemia in about 30%[9] of cases. This complication is impossible to distinguish from true leukemia.

Whereas in Hodgkin's disease the clinical course in adults and children is similar, in lymphosarcoma, with the exception of giant follicle lymphoma, there are characteristic and important differences. There is an acceleration of the pathologic process in children, with advanced local disease often causing death before dissemination. Thus local complications such as superior vena cava obstruction and tracheal compression are more common. This higher biologic activity also manifests itself in a leukemic transformation rate double that seen in adults.[10] Acute leukemia usually results in children whereas chronic lymphatic leukemia more commonly results in adults. Because of this increased rate of progression, the median survival in children is found to be 7.5 months compared to 27 months in adults.[13] Lymphosarcoma in children has a predilection for certain primary sites. Presentation with abdominal symptoms occurs twice as frequently in children as in adults, with intussusception occurring not uncommonly. Symptomatic obstruction of the superior vena cava is reported to be four times as common in the pediatric age group.[10] Reticulum cell sarcoma occurs far more often in bone in children and it appears to be more radiosensitive in this location. In addition, metastases occur later, and it appears potentially curable by aggressive surgery.[10 13]

There are few distinctive haematological findings initially. Abnormal antibody production may cause an acquired hemolytic anemia. Typical findings of acute lymphatic leukemia in both the peripheral blood and the marrow occur when the disease enters the leukemic phase.

DIAGNOSIS

The diagnosis and extent of disease is established as in Hodgkin's disease. Peripheral blood smears and bone marrow examination are necessary to determine if leukemia is present or imminent.

PROGNOSIS

Unlike Hodgkin's disease, lymphosarcoma in children carries a more serious prognosis than in adults. The five year survival is about 10%[9] compared to the adult rate of about 28%.[10]

There are several factors important in the prognosis of lymphosarcoma. Leukemic transformation changes the prognosis markedly since the outlook becomes that of acute lymphatic leukemia. Primary involvement of special organs such as the pharynx, testes, and eye, and of peripheral nodes indicates a better prognosis, whereas mediastinal and abdominal tumours have a less favourable prognosis. Of the histological types, reticulum cell sarcoma and lymphoblastic lymphosarcoma have the least favourable prognosis, and lymphocytic lymphosarcoma and giant follicle lymphoma have the better prognosis. Clinical staging also is important in the out-

look. In adults it has been determined that the five year survivals for stages I, II, and III are 51%, 23% and 5% respectively.[12]

Treatment

The treatment of lymphosarcoma is basically like that of Hodgkin's disease. Intensive therapy is directed at localized disease in the hope of a long remission or possibly a cure, and systemic chemotherapy is used when widespread disease is present.

In localized lymphosarcoma the possibility of radiocurability exists, and thus high doses of radiation to prevent recurrences are necessary. The value of prophylactic irradiation to uninvolved nodes is open to question as suggested in a recent retrospective study.[12] However, until prospective studies are completed, it may be detrimental to deprive patients of prophylactic irradiation. For localized gastrointestinal involvement, surgery may be the method of choice.

Chemotherapy is most commonly employed in advanced disease with constitutional manifestations. It is also useful when prompt regression of a tumour pressing on a vital structure is necessary. For producing remissions in lymphocytic and lymphoblastic lymphosarcoma, chlorambucil, high doses of prednisone (30 mg/day p.o.), and cyclophosphamide, (Procytox) are effective. Reticulum cell sarcoma responds well to vincristine sulphate and also responds to cyclophosphamide. Giant follicle lymphoma improves with chlorambucil. For rapid shrinkage of lymphosarcoma compressing vital structures, nitrogen mustard may prove rapidly effective in as many as 50% of cases.[14]

Drug	Induction dose	Maintenance	Toxicity
Nitrogen Mustard	0.4 mg./kilo I.V.	no	nausea, vomiting leukopenia thrombocytopaenia
Cyclophosphamide	15 mg./kilo I.V./wk. or 2.5 mg./kilo oral	daily	nausea, vomiting alopecia, dysuria leukopenia
Chlorambucil	0.1 - 0.2 mg./kilo/day orally	daily	leukopenia
Vinblastine Sulphate	0.15 mg./kilo up to max. of 10 mgm wkly.	q. 1-4 weeks	marrow depression alopecia
Vincristine	0.07 mg./kilo I.V./wk.	q. 2 weeks	local reaction, alopecia, nueromuscular toxicity, leukopenia.

ACKNOWLEDGEMENT

The author wishes to thank Dr. R. E. Alison and Dr. M. Sonley for their assistance in the preparation of this article.

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Malignant Soft Tissue Tumours In Children

L. Brenner 6T7

INTRODUCTION

The term, "soft tissues", refers to the connective tissue framework of the body plus the organs of locomotion (except bone and cartilage) and their various component structures such as nerves and blood vessels.[16] Despite the fact that the soft tissues make up over 50% of the body weight (the muscles alone constitute 25% of the child's weight[11]), they give rise to malignant tumours relatively infrequently. Only recently has an adequate classification of these sarcomas become available and criteria for their diagnosis still remain controversial. As Stout points out:

The failure properly to label the soft tissue tumor, especially the malignant ones, has led to a great deal of confusion regarding the distribution, relative frequency, and relative malignancy of many of them. This has been largely responsible for the fact that mesenchymal tumours of the soft tissues . . . are the least understood and probably the most inadequately treated of all tumours.[19]

An added difficulty is the fact that two neoplasms, although histologically identical, may differ tremendously in their biological behaviour if one occurs in a child and the other in an adult. Pediatric tumours may appear strikingly bizarre under the microscope and yet be benign; similarly, innocent-appearing tumours may produce deadly metastases.

It is beyond the scope of this article to describe all the soft tissue tumours. Instead, only rhabdomyosarcoma will be discussed in detail. Furthermore, the lymphomas, considered by most authors to be of soft tissue origin, will be omitted since they form a separate field of study.

ETIOLOGY AND PATHOGENESIS

Cohnheim's theory of cell rests[4] appears to be applicable to a group of soft tissue tumours which can be considered truly pediatric.[10 11 21] This theory is based on the premise that neoplasms result from groups of cells which have been misplaced during embryonal development or from cells normally present which have retained their embryonal potentialities. The etiologic agent which causes these cells to proliferate is as yet unknown although there is evidence to implicate viruses, chemicals, and hormones.

A second group of soft tissue tumours is comprised of essentially adult malignancies, their occurrence in children being extremely rare. Suggested causative factors operating in children afflicted with these cancers include noxious agents, infection, and trauma, all of which stimulate fibrous propagation. Chronic irritation probably plays an important part. Premature aging of particular tissues due perhaps to inborn errors of metabolism may also be involved.[11]

CLASSIFICATION

The classification given in Table I is based mainly upon Stout (as adapted by Pack and Ariel[11 12]) and partly upon Shuman[16]:

Type of Tissue	Malignant Tumour
1. Fibrous Tissue.	a) Fibrosarcoma b) Dermatofibrosarcoma Protuberans.
2. Undifferentiated Mesenchyme	a) Malignant Myxoma b) Malignant Mesenchymoma (mixed mesodermal tumour).
3. Heterotopic Bone and Cartilage.	a) Osteogenic Sarcoma (extraosseous) b) Chondrosarcoma (extraosseous).
4. Adipose Tissue.	Liposarcoma.
5. Blood and Lymph Vessels.	a) Angiosarcoma b) Lymphangiosarcoma c) Angioendothelioma d) Kaposi's Sarcoma e) Haemangiopericytoma.
6. Synovial Tissue.	Malignant Synovioma (Synovial Sarcoma).
7. Smooth Muscle.	Leiomyosarcoma.
8. Striated Muscle.	Rhabdomyosarcoma.
9. Mesothelial Tissue.	Malignant Mesothelioma.
10. Tumours of Undetermined Origin.	Malignant Organoid Granular Cell Myoblastoma (alveolar soft part sarcoma).
11. Peripheral Nerves (nerve sheath type).	a) Malignant Neurofibroma (neurogenic sarcoma; neurofibrosarcoma) b) Malignant Schwannoma (malignant neurilemmoma).

TABLE I. Classification of Malignant Soft Tissue Tumours.

INCIDENCE AND RELATIVE DISTRIBUTION

The Tumour Registry at the Hospital for Sick Children in Toronto lists all malignancies diagnosed by biopsy or at autopsy in that hospital. It also includes tumour biopsies received from other Ontario centres for consultation. From 1919 to May, 1965 sixty-two cases of malignant soft tissue tumour were collected.[20] Another fifty-eight cases were designated unclassified sarcomas. A further breakdown of these 120 cases is given in Table II.

Histologic Type of Tumour	Number
1. Sarcoma of Undetermined Histogenesis.	58
2. Rhabdomyosarcoma.	30
3. Fibrosarcoma.	13
4. Lymphangiosarcoma.	5
5. Neurofibrosarcoma.	3
6. Malignant Mesenchymoma.	3
7. Fibromyxosarcoma.	2
8. Haemangiosarcoma.	2
9. Leiomyosarcoma.	2
10. Synovial Sarcoma.	1
11. Myosarcoma.	1

TABLE II. Incidence of Soft Tissue Tumours at the Hospital for Sick Children in Toronto (1919 — May, 1965)

The reported incidence in children, however, varies with different hospitals, one reason being selective admissions. In eight separate studies of pediatric malignancies, in which a total of 1966 children were seen, soft tissue tumours made up an average of 13.8% of the cases.[11] However, the reports ranged from 2.4% to 33% with a median figure of 12%. One can see that soft tissue tumours form a significant percentage of malignancies in children although they are responsible for only about 1% of adult cancers.[9] Of course, the total number of these tumours is higher in adults than in children in keeping with the fact that the overwhelming majority of malignant growths arise in the older age group.

Each of the malignant soft tissue tumours listed in Table I has occurred in children although many are extremely rare in this age group. Rhabdomyosarcoma was by far the most frequently seen soft tissue tumour at the Hospital for Sick Children; fibrosarcoma was a distant second.

GROSS APPEARANCE

In general, a malignant soft tissue tumour has a fleshy appearance. It forms a bulky mass which is fairly sharply demarcated from the surrounding tissue. The cut surface is homogeneous unless degenerations occur. The growth of the tumour may outstrip its blood supply with resulting infarction. Necrosis, mucoid or myxomatous softening, and actual liquefaction are frequent. Haemorrhage from the abundant and very thin-walled blood vessels is not uncommon.[3]

MICROSCOPIC APPEARANCE

The less differentiated forms are highly cellular with scanty stroma. With greater differentiation, the stroma becomes more abundant and characteristic. Numerous blood vessels, often mere capillaries or sinusoids, penetrate the tumour. The type cell may be the fibroblast, osteoblast, rhabdomyoblast, etc. but is often difficult, if not impossible, to recognize. Many of these tumours show a variety of cells.[3]

Recently, Stembridge et al. have examined seven types (sixteen cases) of malignant mesenchymal neoplasm with the electron microscope.[17] They compared the ultrastructural features of the neoplastic cells and their extracellular products with their normal counterparts and found that the tumour cells retained, to an extent proportional to the degree of malignancy, the morphological features of normal cells. They therefore feel that the electron microscope will contribute to the more accurate histogenic identification of these tumours.

TREATMENT

The treatment of choice for almost all soft tissue tumours is prompt radical surgery.[5 9 11 12 19] Often, however, surgery is not feasible because of the extent or location of the tumour. In such cases radiotherapy, alone or in conjunction with less extensive surgery, chemotherapy, or both, has been used with some success.

Tumours of fibrous tissue origin differ somewhat from other soft tissue tumours. There is much controversy regarding which are benign and which are malignant, or, for that matter, which fibrous lesions are even tumours. The diagnosis of "fibrosarcoma" is made not infrequently. Nevertheless, truly malignant fibroblastic tumours capable of metastasizing are relatively rare, particularly in children; hence the present trend is toward conservatism.[10]

PROGNOSIS

The prognosis depends upon the type and location of the tumour, and upon treatment. Of fifty-one children studied by Pack and Ariel, sixteen were living, apparently without recurrence, five years and more after treatment, and another eight were living apparently without residual tumour less than five years after treatment. Five more cases were indeterminate. In children, malignant synovioma had the best prognosis (67% survival rate), followed by liposarcoma (57.1%), rhabdomyosarcoma and fibrosarcoma (each 50%), and malignant neurilemmoma (28.6%). As to tumour site, the highest mortality occurred in patients with sarcomas of the lower extremity, shoulder or torso while the lowest mortality occurred in those with tumours of the hand or arm. Patients undergoing prompt radical surgery had the best prognosis.[11]

RHABDOMYOSARCOMA

A) Definition

A rhabdomyosarcoma is a malignant tumour arising from striated muscle cells.

B) Incidence

As table I indicates, thirty of the sixty-two diagnosed soft tissue tumours seen at the Hospital for Sick Children were rhabdomyosarcomas. Nine other cases were considered probable rhabdomyosarcomas but a definite diagnosis could not be made. There were seventeen males as opposed to thirteen females. The age of the patient at the time of diagnosis varied from birth to fourteen years with the average age being forty-five months.

C) Classification and Description

The classification which best fits the clinical picture is the one given by Horn and Enterline.[8] They divide rhabdomyosarcoma into four types: adult pleomorphic, alveolar, embryonal and botryoid.

1. *Pleomorphic Rhabdomyosarcoma*

Pleomorphic Rhabdomyosarcoma was originally considered to be the only existing form of rhabdomyosarcoma but is now known to be the rarest of the four types. It occurs in adults rather than in children.

2. *Alveolar Rhabdomyosarcoma*

Alveolar rhabdomyosarcoma, first reported by Riopelle and Thériault,[15] is the least known and most recently described group. In a series of sixty-seven cases cited by Shuman,[16] 36% were observed in the first decade of life and 58% within the first two decades. This tumour has a slightly higher incidence in female than in male children. The lesions present in the extremities or in the head and neck with equal frequency but can occur elsewhere. They often originate in skeletal muscle but frequently originate elsewhere.

Clinically, the typical patient complains of severe, intermittent or persistent pain in the affected area, sometimes for months before a mass becomes palpable, but he may present with small, symptomless swellings in the superficial muscles.

Grossly, the tumour is usually firm and nodular but may be soft and fleshy. The cut surface is grey-white or pink in colour and sometimes almost cartilaginous in consistency but cystic areas filled with jelly-like material or turbid fluid may be present.

Microscopically, this variety of rhabdomyosarcoma is characterized by a prevailing alveolar pattern somewhat reminiscent of an adenocarcinoma. However, a variety of histological patterns present themselves in different areas of the tumour. Neoplastic cells sometimes form pseudorosettes around blood vessels or align themselves in papillary formation. Trabeculae of connective tissue of varying vascularity and delicacy have been described as separating alveoli but many of these trabeculae have since been shown to be giant muscle fibers whose nuclei are located in lateral extensions of sarcoplasm. The alveoli themselves are loosely filled with large, oval or rounded, uninuclear cells similar to reticulum cells. These cells contain a variable amount of eosinophilic cytoplasm, sometimes with vacuolations. Occasionally, multinucleated giant cells, polyhedral cells, tadpole-shaped cells, or strap cells with multiple nuclei are observed. Longitudinal and cross-striations are demonstrable in many cases but not in all. Because of its diffuse round cell population, its radiosensitivity, and its tendency to invade the regional lymph nodes, alveolar rhabdomyosarcoma is also often confused with malignant lymphoma.

3. *Embryonal Rhabdomyosarcoma*

This group was originally described by Stobbe and Dargeon.[18] Of thirty-nine cases of rhabdomyosarcoma reported by Horn and Enterline,[8] thirteen were classed as embryonal. Eight of these occurred in males and five in females, the average age being 8.9 years. The head and neck are the most common sites, the lesions usually involving the orbit. Next in frequency is the genitourinary tract, especially the vagina, bladder and spermatic cord. A small number occur elsewhere.

Grossly, the tumour appears as a soft, nodular, unencapsulated lesion varying in colour from grey-white to light yellow and varying in size and extent of invasion and necrosis.

Microscopically, the basic cell type is a long, slim spindle tapering to thin, bipolar processes. The nucleus is usually single and central, the cytoplasm eosinophilic and relatively abundant. The cells may appear tadpole-shaped. Often round cells like those seen in alveolar rhabdomyosarcoma may be numerous.

4. *Botryoid Rhabdomyosarcoma*

Horn and Enterline's series of thirty-nine cases of rhabdomyosarcoma included five designated as botryoid. The ages ranged from ten months to seventeen years, the average being seven years. Four of the five patients were males.

The gross lesion is a large, oedematous, polypoid, unencapsulated tumour of soft or gelatinous consistency. It usually arises just beneath the mucous membrane of a hollow viscus or body cavity rather than within muscle.

Histologically, botryoid rhabdomyosarcoma appears similar to the embryonal type. One diagnostic feature, however, is the presence just beneath the mucous membrane of a multilayered band of cells—the "cambium layer" of Nicholson. These cells are described as being indifferent short spindles with relatively little cytoplasm, lying parallel to the surface of the lesion. Although fairly uniform, they show a high rate of mitotic activity. Unfortunately, this feature is not always well developed.

Recently, by means of a fluorescent antibody technique, some cells have been shown to contain myosin.[7]

D) Mode of Spread

Rhabdomyosarcomas grow rapidly and invade the surrounding tissues. Furthermore, they tend to metastasize widely both by hematogenous and lymphogenous routes. The most frequent sites of metastases are lungs, liver, skin, subcutaneous tissue and lymph nodes.

E) Treatment

The treatment of choice for all forms of rhabdomyosarcoma is immediate radical surgery whenever possible.[1 8 13 14] Although radiation therapy produces temporary palliation in about one-half of patients with rhabdomyosarcoma,[14] irradiation alone results in few long-term survivals.[1] Some rhabdomyosarcomas in children have proven sensitive to Actinomycin D and other chemotherapeutic agents,[1 13] the tumour in one inoperable case regressing sufficiently to make radical surgery possible.[14] If metastases occur, Actinomycin D combined with radiotherapy is useful in controlling them.[5]

F) Prognosis

The prognosis is grave but can be improved with proper treatment. Michael states that the average duration of life with the embryonal type is approximately ten to twelve months after diagnosis, while the average expectancy after discovery in the alveolar type is thirty months.[10] Pack and Eberhard, however, report a five year "cure" in twenty-two of sixty-five cases (34%) in which treatment was aggressive.[11] Twenty or fifty-five patients with embryonal or alveolar phabdomyosarcoma (36%) seen at the M.D. Anderson Hospital were living tumour-free at least three years after diagnosis, and some up to eleven years.[1] Of twenty-four patients with botryoid, alveolar or embryonal rhabdomyosarcoma collected by Horn and Enterline, four were still alive from nineteen months to twelve years after prompt aggressive surgery. These four represented nearly 50% of the patients in whom radical surgery was undertaken immediately.[8]

SUMMARY

An attempt is made to define and to classify malignant tumours of soft tissue origin. Their general characteristics in children are then described. Rhabdomyosarcoma, one of the soft tissue tumours, is described in detail with particular reference to its pathological description. The experience of the Hospital for Sick Children with regard to incidence of soft tissue tumours is presented and compared with reports in the literature.

ACKNOWLEDGEMENT

The author is indebted to Dr. T. C. Brown and his staff in the Pathology Department of the Princess Margaret Hospital for their helpful criticism and suggestions in the preparation of this article. The author also wishes to thank Dr. W. L. Donohue fo the Hospital for Sick Children for permission to use the Tumour Registry.

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Abstract

The Treatment of Acute Myocardial Infarction
David L. Watt, M.D., F.R.C.P.(C): Applied Ther., Vol. 7, No. 4, April 1965, pp. 295 - 299.

The best treatment of acute myocardial infarction is in a cardiac intensive care unit. The unit at Sunnybrook Hospital is briefly described.

UNCOMPLICATED ACUTE MYOCARDIAL INFARCTION

Relief of severe chest pain. Morphine, Pethidine, Pantopon(R) subcutaneous or I. V., if necessary, are useful. Oxygen, even in the absence of dyspnea, may relieve the pain. Anxiety is treated with phenobarbital, meprobamate and reassurance. In the acute stage, complete rest is necessary. During the next three or four weeks bathroom privileges are allowed, then gradual ambulation over the next week. Diet, fluids initially, then a soft diet for a few days, then a full diet. With evidence of heart failure, salt is restricted. *Anticoagulants.* The efficacy of these drugs is questioned by several authors but others feel that they reduce the incidence of thromboembolic phenomena. In the absence of contraindications such as, bleeding tendencies, hypertension, hepatic or renal diseases, this author recommends oral anticoagulants, the choice of which is left to individual preference. Prothrombin times should be checked daily.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Heart failure. Salt should be restricted in all cases and oxygen administered if there is any dyspnea. For mild pulmonary congestion, mercaptomerin sodium (thiomerin(R)), 2 cc. subcutaneously, q.48 h. for the first few days may suffice. Digitalization may be necessary. Digoxin is recommended. Digitalizing dose: 0.5 mg. q.6 h. X 3 doses. Maintenance dose: 0.25 to 0.5 mg. daily. For acute pulmonary edema, prompt aminophylline, mercaptomerin (thiomerin(R)). Rotating tourniquets or venesection may be helpful. Hypotension without shock responds to relief of pain and anxiety. On the other hand, shock requires special treatment. An inotropic drug such as methamphetamine hydrochloride (methedrine(R)) 15 mg. subcutaneously is given. If this fails, an I. V. infusion of metaraminol bitartrate (aramine(R)) or levarterenol bitartrate (levophed(R)) to maintain systolic pressure at 100 mm. of mercury without excessive administration of fluid is begun.

ARRHYTHMIAS

Atrial premature beats are not usually of serious significance and no treatment is required. Ventricular premature beats are common and may precede ventricular tachycardia or ventricular fibrillation. They are treated with pronestyl, 250 - 500 mg. orally or I. M. q.6 h. or quinidine sulfate, 3 - 6 gr., orally q.6 h. Treat atrial fibrillation and flutter with digitalis if the ventricular rate is rapid. When atrial tachycardia with various degrees of A-V block is due to digitalis (with or without diuretics), then treatment consists of its withdrawal and the oral administration of potassium. If the patient is very ill and serum K is low, then 40 mEq. of KCl may be given slowly I. V. in 500 c.c. of 5% glucose in water. When atrial tachycardia is not due to digitalis, it may be aborted by vagal stimulation. Failing this, digitalization is indicated. In the presence of partial A - V block, withhold digitalis and monitor the ECG. Complete A - V block is a serious complication but is reversible if the patient survives the acute phase. Administer isoproterenol (isuprel(R)) 10 - 20 mg. sublingually, q.2 h., p.r.n. in order to speed up the idioventricular rhythm. If this is ineffective, the drug can be given I. V., 1 - 2 mg. in 500 c.c. of 5% glucose in water.

Hydrocortisone enhances A - V conduction. The dose is 100 mg. direct intravenous injection followed by 200 mg. in 500 c.c. of 5% glucose in water every 8 hours for the first day, then oral steroids gradually decreased over the next two weeks. These methods failing, electrical pacing is indicated. Ventricular tachycardia must be corrected promptly. Procaine amide (pronestyl(R)) 1 g. in 100 c.c. of 5% glucose in water is infused I. V. under ECG control. Hypotension is treated with vasopressors. If necessary, cardioversion under light pentothal anesthetic is carried out.

CARDIAC ARREST

External cardiac, massage is begun immediately. A second operator starts artificial respiration. An ECG is obtained. Once circulation and respiration are under control; specific therapy can be started. An external pacemaker should be tried briefly. Failing this, 1 c.c. of epinephrine 1: 10,000 solution is given by intracardiac injection. Review the effectiveness of cardiac massage and condition of the airway. Correct acidosis with 300 c.c. of 5% sodium bicarbonate I. V., as soon as practical. Following the bicarbonate, the pacemaker and the epinephrine may be tried again. Ventricular fibrillation is treated by electrical defibrillation as soon as possible. Bicarbonate, then procaine amide are administered and electrical defibrillation attempted at each stop. Epinephrine, as above, is given if the amplitude of the fibrillatory waves decreases.

THROMBOEMBOLISM

Pulmonary Embolism. Prevention: Anticoagulant therapy and active movement in bed. Treatment: oxygen for dyspnea, narcotics for pain. Systemic emboli may be treated surgically according to their site of impaction and the clinical course.

OTHER COMPLICATIONS

A persistent pericardial friction rub is treated by salicylates and steroids. Cardiac aneurysms are treated surgically. Rupture of the myocardium into the pericardial sac causes sudden fatal cardiac tamponade. Rupture of the interventricular septum or rupture of a papillary muscle may be surgically correctible.

SUMMARY

The mortality of patients with acute myocardial infarction is between 30 and 40%. Two-thirds of the deaths occur in the first forty-eight hours.

M.L.S.

1952-1964 - No kidney damage - No teeth mottling - No liver impairment - No bone marrow depression - No blood dyscrasia - No neurotoxicity - No photosensitivity. **ERYTHROCIN*** (Erythromycin Abbott) for 8 out of 10 everyday bacterial infections, you can't prescribe a safer, more effective antibiotic.

PRECAUTIONS: Side effects are rare. If a patient should show signs of sensitivity, countermeasures (e.g., epinephrine, steroids, etc.) should be administered and the drug withdrawn. DOSAGE: Usual dose is 250 mg. q.i.d. Children's dosage based on body weight.

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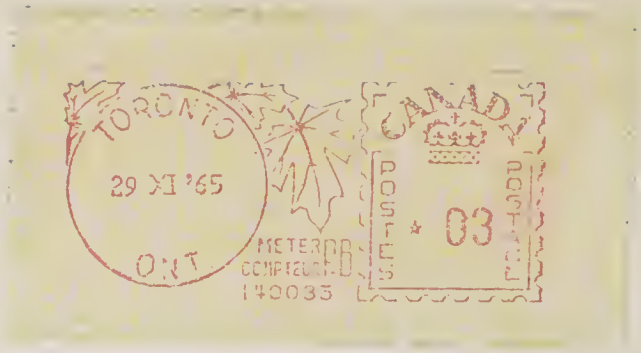

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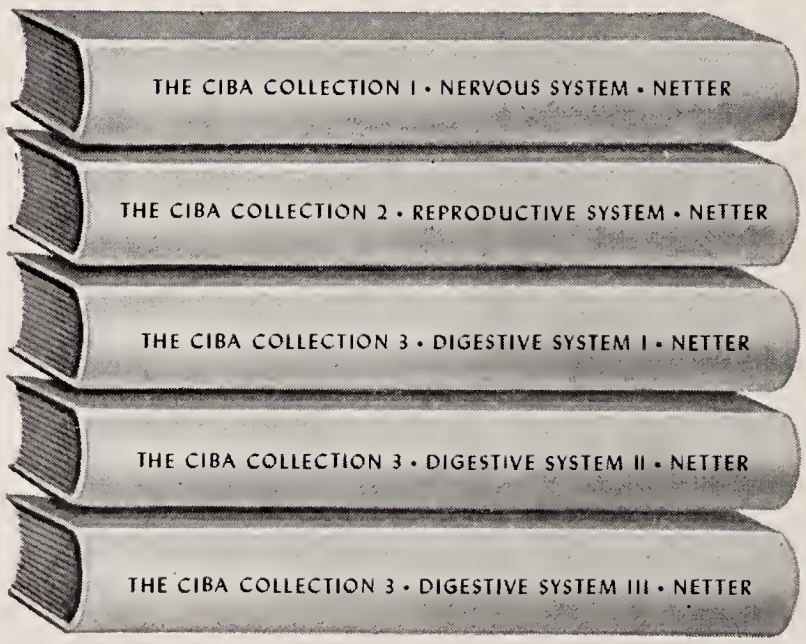
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